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Volume 84 Number 5 May 1997

The British Journal of SURGERY

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37

RMATION
Tazocin is a broad spec-
ericidal penicillin for the
of the following infections
sensitive bacteria:- lower
y tract infections, urinary
ctions, intra-abdominal infec-
n infections, septicaemia and
bic intra-abdominal, skin and
espiratory tract infections;
with impaired host defences.
(intravenous use only):
elderly/children over 12:
4.5g every 8 hours (range from
5g every 6-8 hours dependent
severity). *Children:* No data to
t use. *Renal Impairment:*
reduction may be necessary,
consult data sheet. Contra-
tions: Hypersensitivity to peni-
cephalosporin or ß-lactamase
tors. Warnings: Discontinue if
hylactic or allergic reaction
rs. Precautions: Periodic assess-
of renal, hepatic and haemato-
cal function advised. Discontinue
bleeding manifestations occur.
istant bacteria may cause superin-
tion. Convulsions may occur with
her than recommended doses.
sibility of hypokalaemia in patients
h low potassium or on cytotoxics or
retics. Evaluate patients for
hilis prior to treatment for gonor-
oea. Use during pregnancy or lacta-
n: Only if benefit outweighs risk.
de-effects: Most frequent: gastro-
estinal disturbances; various skin
ctions including rashes, erythema,
ritus and urticaria; allergic reac-
ns; superinfection; phlebitis, throm-
phlebitis, pain/inflammation at site
injection. Less frequent: muscle
in or weakness; hallucination; dry
uth; stomatitis, sweating; oedema;
edness and rarely leucopenia, inter-
tial nephritis. Haematological
anges, increases in liver and rarely
al function test values have been
orted. Overdose: Piperacillin may
reduced by dialysis. Presentation:
zocin 2.25g: Vials containing
eracillin 2g (as *piperacillin sodium*)
d tazobactam 250mg (as tazobactam
dium). Tazocin 4.5g: Vials containing
eracillin 4g (as piperacillin sodium)
d tazobactam 500mg (as tazobactam
dium). Basic NHS Price: 4.5g
ength:- single vial £13.16, single
usion pack £14.48; 2.25g strength
gle vial £7.24. PL nos: 4.5g strength
0095/0254; 2.25g strength PL
95/0252). PA nos: 4.5g vials
/68/2; 4.5g combipack 37/68/3;
25g vial 37/68/1. Legal Category:
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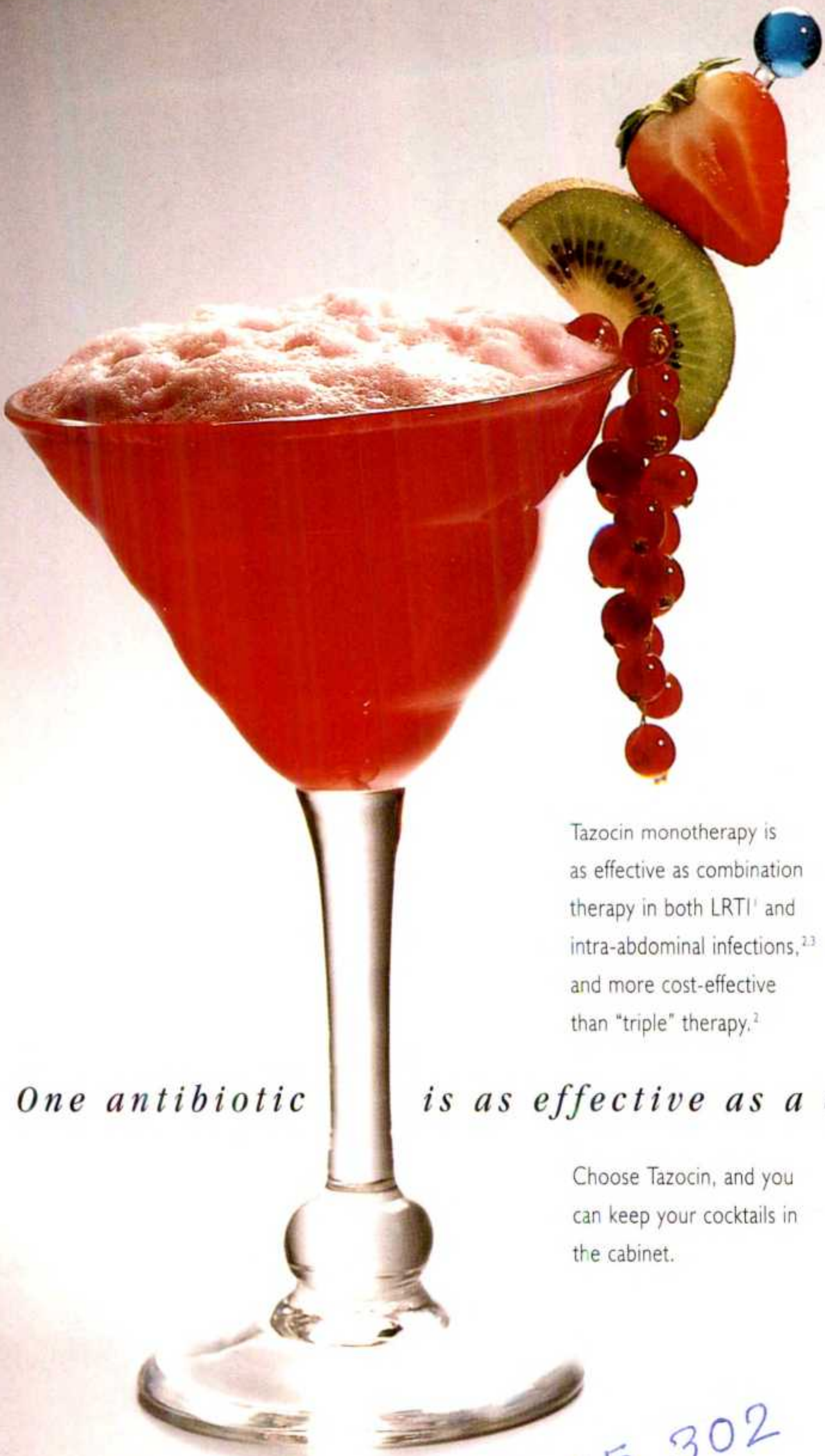
nited, Cyanamid House, Fareham
ad, Gosport, Hampshire, PO13 0AS.
rade mark.
FERENCES: 1. Pallett AP. ICID, Prague
94; Abstract 857. 2. Ravichandran D. Br
Surgery 1994; 81 (Suppl 1): 75. (102185)
Huizinga WKJ. 7th European Congress of
nical Microbiology and Infectious
eases, Vienna 1995: Abstract 573.
te of preparation: March 1996.

Wyeth Lederle



Tazocin monotherapy is as effective as combination therapy in both LRTI[1] and intra-abdominal infections,[2,3] and more cost-effective than "triple" therapy.[2]

One antibiotic is as effective as a cocktail

Choose Tazocin, and you can keep your cocktails in the cabinet.

P, 25,302

TAZOCIN*
(piperacillin/tazobactam)

Solo power in polymicrobial infections

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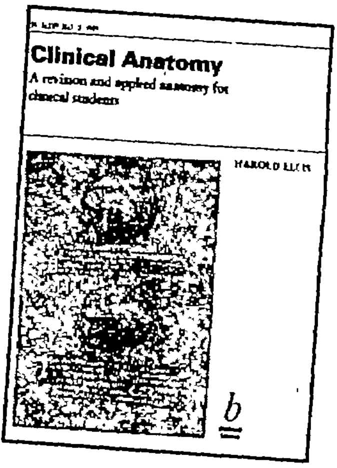

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British Journal of Surgery 1997, **84**, 593–594

Leading articles

Bowel ischaemia after aortoiliac surgery

Bowel ischaemia after reconstructive aortoiliac surgery is a disaster, and when it progresses to perforation the mortality and morbidity rates are high. Variation in reported incidence can be explained by differing diagnostic aggressiveness; routine postoperative colonoscopy gives the highest yield. It can also be due to variation in the selection of patients, most reports coming from highly specialized centres. From the Swedvasc registry it has been possible to obtain an estimate of incidence which probably reflects a true value for unselected operations, as virtually all vascular surgery in all categories of hospitals in Sweden is included[1]. By scrutinizing all patient records and by various validation procedures the incidence was calculated as 2·8 per cent[2]. The highest frequency was noted in patients with ruptured aneurysm who developed shock (7·3 per cent). Developing bowel ischaemia in this situation increases the mortality rate by about 20 per cent.

Using the Swedvasc registry data to compare hospital records of patients developing ischaemia with a random sample of records of patients without this complication has allowed an analysis of risk factors[3]. Kidney disease, emergency surgery, age, surgery at a regional hospital, aortobifemoral graft, operating time, cross-clamp time and ligation of one or both internal iliac arteries were independent risk factors for the development of postoperative bowel ischaemia. While the clinical manifestation of bowel ischaemia after aortoiliac surgery is not common, it is difficult to diagnose if it is not considered. With our present knowledge we may make some practical comments on the management of this condition.

Implantation of the inferior mesenteric artery into the graft has never been shown to have a preventive effect on the development of bowel gangrene. On the other hand, it seems of great importance that at least one internal iliac artery is vascularized[3]. It is not possible to avoid bowel ischaemia by using the new stent graft systems[4], but the incidence is not yet known because available series are still too small.

Prolonged operation time and aortic cross-clamp time are independently associated with bowel ischaemia[3]. Preoperative shock and intestinal traction during the surgical procedure may result in a low-flow situation. The two important mechanisms causing bowel ischaemia are primary ischaemic insult during cross-clamping and reperfusion injury. Animal experiments have indicated that primary ischaemic injury is the more important mechanism after total ischaemia, whereas reperfusion injury is more important in situations of low flow. Endogenous scavenging antioxidants are depleted during cross-clamping and, although final proof is lacking, there are data indicating that substances with scavenging effects, such as mannitol, may have a protective effect on the intestinal mucosa.

The effect of vasoactive drugs in intestinal ischaemia is controversial. Manufacturers have claimed that low-dose dopamine and dobutamine increase intestinal blood flow but there is mounting evidence that these agents may cause or increase bowel ischaemia[5]. In a prospective randomized study on elective abdominal aneurysm surgery, patients receiving low-dose dopamine had significantly lower sigmoid intramucosal pH than controls[6]. This issue is complicated by the fact that patients in shock will receive vasoactive drugs, and operation for a ruptured aneurysm in shock is a great risk *per se*[3].

In a case–control study bowel ischaemia was found in patients who had received more α-adrenergic agonists[7]. Patients with bowel ischaemia also had significantly lower perioperative cardiac output. In a large combined cohort and case–control study this issue proved to be complex – a multifactorial clinical situation with multipharmacy[3]. Vasoactive drugs should be used on strict indications and with relevant haemodynamic monitoring. Low cardiac output is by no means an alternative.

A high index of suspicion is perhaps the most important route to an early and correct diagnosis. This means suspicion in patients whose postoperative course does not progress normally, especially when there is early passage of stool or blood in the stool. The cardinal symptom mentioned in textbooks, early bloody diarrhoea, is noted in only one-quarter of affected patients[2].

It is important to appreciate that 95 per cent of ischaemic lesions are within the diagnostic reach of a flexible sigmoidoscope[2]; when the suspicion arises there is, therefore, a simple diagnostic method in the majority of patients. On the other hand, there is no indication for routine sigmoidoscopy which would detect patients with mucosal lesions that will heal. In selected patients, especially those with ruptured aneurysm, measurement of sigmoid intramucosal pH[8] offers a possibility of non-invasive and continuous monitoring. A pH below 7·1 is an early warning sign, and at pH below 6·9 ischaemic colitis is a likely diagnosis and sigmoidoscopy should be performed[9]. When gangrene develops the pH value is persistently below 6·8.

In patients with manifest bowel gangrene the treatment is a straightforward resection of the affected bowel, leaving a stoma; in most patients this is Hartmann's procedure. A problem which may be encountered when diagnostic activity in the form of sigmoidoscopy is high is the detection of a number of mucosal lesions, the majority of which will heal without gangrene or perforation. Routine sigmoidoscopy shows some degree of ischaemia in as many as 10 per cent of patients having elective aortoiliac surgery and in many more after surgery for ruptured aneurysm[9,10]. In such circumstances, intramucosal pH monitoring may be helpful in preventing unnecessary relaparotomy but, otherwise, laparotomy should be used liberally when there is doubt about the correct diagnosis and when there is deterioration during conservative management.

In conclusion, bowel ischaemia after aortoiliac reconstructive surgery represents a major challenge. It is especially prevalent after operation in patients who are shocked because of ruptured aortic aneurysm. A high degree of suspicion should allow a correct diagnosis, flexible sigmoidoscopy being the diagnostic method of choice in the majority of cases. In unclear situations tonometric measurement of intramucosal pH may be helpful in deciding whether to perform laparotomy. In most cases Hartmann's procedure is the optimal treatment option, if necessary in combination with graft removal and an extra-anatomic reconstruction.

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The magnetic resonance operating theatre

Magnetic resonance imaging (MRI) is now an established radiological tool; it was developed in the late 1970s and came into clinical usage in the early 1980s. Its major advantage over other radiological methods is the ability to produce very high-quality soft tissue images without the need for ionizing radiation. MRI can be used in pregnancy but is generally avoided in the first trimester. Images can be produced in any specified plane, even in three dimensions. It should be ideal for monitoring surgical treatment, particularly using the very fast new pulse sequences which produce images every 1·5 s. The extent of tissue damage produced at interventions using laser, cryotherapy, focused ultrasound or radiofrequency waves can be monitored in 'real time'.

MRI-guided biopsy, notably of the breast[1], has been carried out in conventional scanners using complex stereotactic devices. However, these scanners fully enclose the patient and do not readily allow such interventions. The recent advent of interventional MRI machines has improved the situation. The first open-configuration machine was a 0·067-tesla (T) system (Toshiba, San Francisco, California, USA)[2], featuring two permanent magnets arranged one above the other, held apart by large columns. While this left minimal vertical clearance, there was reasonable access to the lateral aspect of the patient. A similar device, the 0·2-T Magnetom Open (Siemens, Erlangen, Germany), followed[2]. Increased field strength resulted in better images but vertical access was still severely limited. The 0·5-T Signa SP10 machine (General Electric, Milwaukee, Wisconsin, USA), based on two *en face* superconducting doughnut-shaped magnets, has revolutionized access[3], permitting excellent vertical and lateral exposure between the magnets. The patient may be placed supine or prone along the longitudinal axis of the magnets, or perpendicular to it, or seated in various positions within the field. Virtually any anatomical region can easily be reached for interventional procedures. Clinical trials using this type of machine began in Boston in 1994[4].

The introduction of these machines has produced an increased requirement for magnetic resonance-compatible equipment, from simple items such as trolleys to biopsy needles and surgical instruments. Potentially magnetic materials both outside and inside the patient can be dangerous, and even non-magnetic materials placed in the field may have detrimental effects on image quality. There has been some development of magnetic resonance-compatible tools; the first biopsy needle for aspiration cytology, composed of stainless steel with a high nickel content, was designed in 1987[5]. The potential to perform complex procedures under MRI guidance has also prompted the development of magnetic resonance-compatible anaesthetic equipment. It is now possible to provide safe general anaesthesia without the equipment being affected by the scanner's magnetic or radiofrequency fields. Conversely, the electromagnetic fields generated by the new anaesthetic monitoring devices do not affect the magnetic resonance image quality.

A number of interventional procedures have been carried out in these state-of-the-art machines. Real-time image-guided biopsy of abdominal and of head and neck neoplasms has been performed[6]. The technique of 'frameless stereotaxy' is employed, whereby the lesion is imaged beforehand and the needle pathway planned to avoid vital structures. This pathway is then reproduced during the biopsy using a hand-held instrument and real-time image guidance. The exact position of the needle tip is displayed continually on the image by means of 'tip-tracking'. The commonest method of providing such tip control is a computer software triangulation system using light-emitting diodes on the instrument handle and cameras within the magnet bore ('flashpoint tracking'). A new and less restrictive form of tip-tracking uses a miniature radiofrequency coil attached to the end of the instrument[7].

MRI can monitor thermal energy deposition in tissues, a feature that has proved useful in the laser ablation of hepatic malignancies[8]. Real-time imaging has enormous potential for the accurate guidance of destructive energy. Tissue ablation by newer methods, such as cryotherapy, radiofrequency waves and focused ultrasound, can be monitored and has much future potential.

Small-diameter magnetic resonance-compatible endoscopes are now available which allow minimal access techniques to be combined with MRI to assess the operative field and monitor the operation as it proceeds. MRI-guided endoscopic removal of sequestrated intervertebral discs and release of spinal nerve entrapment has been reported[9]. MRI-guided endoscopic sinus surgery has also been performed[10].

The use of MRI during abdominal surgery remains largely unexplored, although one very preliminary study has assessed the magnetic resonance compatibility of some laparoscopic equipment[2]. Potential uses include intraoperative image reconstruction to elucidate complex anatomy (in any plane or in three dimensions); in the biliary tract, for example, this might be combined with magnetic resonance cholangiography. Combined MRI and laparoscopic tumour staging and biopsy, for example for pancreatic carcinoma, should be possible and allow surgical bypass to proceed under the same anaesthetic if the tumour is irresectable. Laparoscopic guidance of interstitial laser fibres into solid tumours may significantly decrease the duration of these procedures.

There are also exciting potential applications in open surgery. Image guidance may be used to assess completeness of tumour or tissue excision, for example of the mesorectum in anterior resection or of renal tumours. Image-guided excision of impalpable breast lesions is another attractive possibility. MRI is already an established technique for imaging anal fistulas and peroperative MRI guidance might act as the surgeon's road-map, making fistula anatomy clearer and surgery safer. Similar possibilities for image-guided minimal access surgical techniques in the thorax and joints need to be explored.

To fulfil such potential, there is a need to develop conventional and laparoscopic instruments that are both inert to magnetism and produce minimal magnetic resonance image degradation. Likely materials for such instruments include plastics, titanium, ceramics and polyetheretherketone (PEEK). A successful PEEK biopsy needle has already been manufactured[7]. Some conventional titanium instruments already exist, but specialist tools, such as fistula probes and retractors, still await development. Once compatible instruments become available, much study will be needed in the field of surgical ergonomics to develop safe protocols for procedures within the magnetic resonance environment. Potential benefits of this new technology to the patient include safer, less invasive procedures, a reduced frequency of hospital visits, reduced inpatient stay, and an increase in the number of procedures that can be carried out on a day-case basis.

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Editors' announcement

British Journal of Surgery on CD-Rom

By now, a CD-Rom containing all the papers published in 1996 should have been received by all subscribers to the British Journal of Surgery. The CD, which functions in both Windows and Macintosh formats, was produced in collaboration with our publishers, Blackwell Science Ltd, and the costs were underwritten by the British Journal of Surgery Society.

The British Journal of Surgery is committed to investigating the various available forms of electronic publishing and already has its own dedicated web site on the Internet (http://www.blacksci.co.uk/products/journals/bjs.htm). Archiving papers from 1996 is an experiment to test the value of the CD format. Later in the year we will be sending all readers a questionnaire to help us assess the usefulness of the CD and to seek opinion concerning future developments. Plans are already in hand to archive 1997 papers on CD and ways of utilizing remaining space on the disk are being discussed.

The British Journal of Surgery Society, through the Journal Editors, would be pleased to receive any comments or suggestions.

J. A. Murie
J. R. Farndon
C. D. Johnson
J. J. Earnshaw
P. J. Guillou

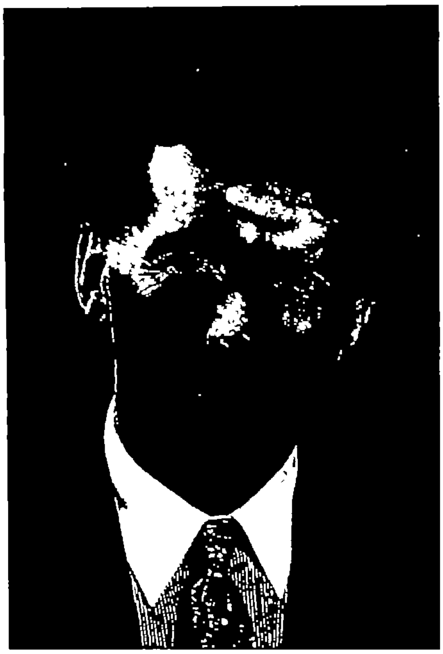
British Journal of Surgery 1997, 84, 598

New Members of the Editorial Board

Continuing our introduction of surgeons from overseas who have joined the Editorial Board of the Journal during 1996. We present a short synopsis of their biographical data and clinical interests.

PROFESSOR CLAUDIO BASSI
(Italy)

Claudio Bassi (born 1952) has been Assistant Professor of Surgery in Verona, Italy since 1988. A graduate of Padua, he obtained further training in Verona before taking up his present appointment. His particular interest is in pancreatic surgery, including acute pancreatitis and infection and pancreatic transplantation; he has written widely on these subjects. He is an Executive Member of the European Pancreatic Club, a Member of the Editorial Board of the *International Journal of Pancreatology* and Secretary of the Associazione Italiana Studio Pancreas.



PROFESSOR ODD SØREIDE
(Norway)

Odd Søreide is Professor and Chief of Department of Surgery B at the National Hospital (Rikshospitalet), University of Oslo. He trained in Bergen (Norway) and London, and served as Professor in Gastrointestinal Surgery at the University of Bergen from 1990 until 1993, when he took up his present appointment. He is Executive Editor of the *Scandinavian Journal of Gastroenterology*. His clinical interests are in hepatopancreatobiliary surgery, liver transplantation and gastrointestinal cancer. He has an interest in medical technology assessment and health-care evaluation.

British Journal of Surgery 1997, 84, 599–602

Review

Open *versus* closed establishment of pneumoperitoneum in laparoscopic surgery

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Background Closed laparoscopy, employing a Veress needle and blind insertion of the first trocar, is favoured by most laparoscopic surgeons. The potential danger of this technique is the occurrence of visceral or vascular injury. Establishment of pneumoperitoneum by an open technique using a blunt-tipped trocar may be a safer alternative.

Methods and Results Retrospective review of the literature and the authors' experience was used to compare closed and open laparoscopy. Data on closed laparoscopy in 489 335 patients and on open laparoscopy in 12 444 patients were culled. Rates of visceral and vascular injury were respectively 0·083 and 0·075 per cent after closed laparoscopy, and 0·048 per cent and zero after open laparoscopy. Mortality rates after closed and open laparoscopy were respectively 0·003 per cent and zero. Pearson χ^2 analysis demonstrated a statistically significant difference in terms of visceral and vascular injury between closed and open laparoscopy ($P = 0{\cdot}002$); there was no such difference for mortality rates.

Conclusion Open establishment of pneumoperitoneum is advocated in laparoscopic surgery because it is safer than the closed method.

The favoured method of establishing a pneumoperitoneum in laparoscopic surgery is the closed technique[1]. This involves insufflation of the peritoneal cavity through a spring-loaded (Veress) needle which is blindly placed intraperitoneally. Subsequently, a trocar is inserted blindly to allow introduction of a laparoscope. Adhesions between viscera and the abdominal wall resulting from previous inflammation or surgery, patients with a thin abdominal wall, and poor technique are factors which predispose to visceral or vascular injury due to perforation by the Veress needle or the first trocar[2]. Such injury may cause major morbidity and even death, particularly when unrecognized at the time of operation.

The open technique is an alternative method of creating a pneumoperitoneum. In this technique the peritoneal cavity is opened under direct vision and a blunt-tipped (Hasson's) trocar introduced[3]. Although the open technique appears to be safer than the closed method, most laparoscopic surgeons prefer to use the Veress needle and insert the first trocar blindly because they feel that the closed technique is faster, requires a smaller incision and is not associated with leakage of carbon dioxide.

At the University Hospital Rotterdam Dijkzigt, the open technique of establishing a pneumoperitoneum was adopted after complications due to insertion of the Veress needle and the first trocar were experienced. The purpose of this study is to assess the complications of closed and open establishment of pneumoperitoneum by reviewing the English literature and the experience at the authors' institutions.

Method of analysis

The English literature on methods and results of creation of a pneumoperitoneum in laparoscopic surgery from 1974 until the present was reviewed. CD-ROM Medline (OVID) database was used as the literature source. The search terms used were: pneumoperitoneum, laparoscopy, Hasson and Veress. The studies reviewed involved laparoscopic surgery performed by either surgeons or gynaecologists. To prevent reviewing studies that reported data on identical patients, only the study with the greatest number of patients per country, in which the type of procedure (surgical or gynaecological) and the period of time were specified, was included in this analysis. Studies that lacked essential information on total number of patients or the method used for creation of a pneumoperitoneum were excluded. The incidence of visceral injury, vascular injury and gas embolism, and mortality rates were documented. Visceral and vascular injuries in patients who had closed laparoscopy were categorized according to lesions resulting from perforation by either the Veress needle or first trocar, when possible. Data on wound infection and incisional hernia at the site of the first trocar were documented. Data on establishment of pneumoperitoneum at the authors' institutions were collected in a similar fashion.

To analyse possible differences in the incidence of visceral and vascular injury, and mortality rate, a Pearson χ^2 analysis was carried out.

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P. 25, 302

Table 1 Visceral and vascular injury, and deaths associated with closed laparoscopy

				No of visceral injuries				No of vascular injuries			
Reference	Year	Procedure	No of patients	Veress	Trocar	Unspecified	Total	Veress	Trocar	Unspecified	Total
Mintz[4]	1977	Gynaecological	99 204	5	26 (2)		31	25	18	–	43
Chamberlain[5]	1980	Gynaecological	50 247			101 (1)	101	–	–	97	97
Lehman-Willenbrock *et al*[6]	1992	Gynaecological	260 206			157 (1)	157	48	107	–	155
Deziel *et al*[7]	1993	Laparoscopic cholecystectomy	77 604			109 (5)	109	35	36 (3)	–	71
Sigman *et al*[8]	1993	Laparoscopic cholecystectomy	781			3	3	–	1	–	1
Present study	1996	Various	1 293	1	2 (1)		3	–	1	–	1
Total			489 335	6	28	370	404	108	163	97	368

Values in parentheses are numbers of deaths

Results

Local study

Closed laparoscopy was used at the authors' institutions in 1293 patients having laparoscopic cholecystectomy, appendicectomy, colorectal procedures, adrenalectomy, splenectomy or diagnostic procedures (*Table 1*). Visceral lesions occurred in three patients. In the first patient the caecum was perforated by the Veress needle. This perforation was not recognized at the time of operation. After operation, abdominal sepsis was evident at 2 days. Multiple laparotomies followed to allow open abdominal lavage. After a hospital stay of 5 months, the patient was discharged. The other two patients with visceral injuries both had peritoneal adhesions due to previous surgery. In both cases the trocar caused a perforation of the bowel. In one patient, the perforation was not recognized during operation. In spite of several laparotomies, this patient eventually died from myocardial infarction. The other patient with a trocar lesion of the bowel underwent direct repair and recovered uneventfully. Vascular injury occurred in one patient; a large branch of the superior mesenteric artery was lacerated by the first trocar, which was a disposable instrument with a safety shield. Emergency laparotomy was undertaken and the injury was repaired. The postoperative course was uneventful. Gas embolism was not observed in any patient. In 15 patients conversion from laparoscopy to laparotomy was necessary because vision was greatly reduced by insufflation of the omentum ($n = 9$) or preperitoneal insufflation ($n = 6$). Wound infection at the site of the first trocar was observed in nine patients but none required surgical drainage. Incisional hernia was noted in three patients (0·23 per cent).

Open laparoscopy was performed in 438 patients for various laparoscopic procedures: cholecystectomy, appendicectomy, colectomy, splenectomy, adrenalectomy, gastric fundoplication and staging of hepatic or pancreatic malignancies (*Table 2*). Visceral or vascular injury due to establishment of the pneumoperitoneum and gas embolism did not occur in any patient. In one patient, who had had several previous laparotomies, access to the peritoneal cavity was not possible because of extensive adhesions between the bowel and the anterior abdominal wall. The median follow-up was 12 (range 1–25) months. Wound infection at the site of the first trocar was observed in four patients. In one case, the infection was caused by a gauze which was left behind in the infraumbilical incision. A haematoma at the site of the first trocar was noted in nine patients; all haematomas resolved spontaneously. Incisional hernia was not observed.

Table 2 Visceral and vascular injury associated with open laparoscopy

Reference	Year	Procedure	No. of patients	No of visceral injuries	No of vascular injuries
Hasson[9]	1975	Gynaecological	150	–	–
Penfield[10]	1985	Gynaecological	10 840	6	–
Perone[11]	1992	Gynaecological	585	–	–
Sigman *et al*[8]	1993	Laparoscopic cholecystectomy	247	–	–
Adana *et al.*[12]	1994	Various	184	–	–
Present study	1996	Various	438	–	–
Total			12 444	6	0

Review of the literature

Closed laparoscopy. Six studies on closed laparoscopy were selected for review. All studies, except for the comparative study by Sigman *et al.*[8], were retrospective analyses. The visceral injuries, vascular injuries and mortality rate of closed laparoscopy in 489 335 patients are shown in *Table 1*. The total incidence of visceral injury was 0·083 per cent (404 of 489 335). The time of recognition of the visceral injury was not reported in most studies. Among the 404 patients with visceral injury, ten (2·5 per cent) died from this complication. The total incidence of vascular injury was 0·075 per cent (368 of 489 335). Of the specified injuries, 39·8 per cent (108 of 271) were caused by insertion of the Veress needle. The location of 38 vascular lesions due to insertion of a trocar was reported: aorta ($n = 13$), inferior caval vein ($n = 5$), iliac artery ($n = 12$), iliac vein ($n = 7$) and mesenteric artery ($n = 1$). Three of 368 patients (0·8 per cent) with vascular injury died from this complication. Gas embolism was reported in four cases and was fatal in all of them. Three other patients who died suddenly during laparoscopy were thought to have died from gas embolism. This gives an incidence of gas embolism in closed laparoscopy of 0·001 per cent (seven of 489 335). In the studies reviewed, the use of either reusable or disposable trocars was not documented consistently nor were trocar injuries stratified for the type of instrument. Wound infection and incisional hernia were not reported consistently.

Open laparoscopy. Six studies on open laparoscopy were reviewed. Except for the comparative study by Sigman *et al.*[8], all were retrospective. The visceral and vascular injuries, and mortality rates, of open laparoscopy in 12 444 patients are shown in *Table 2*. The total incidence of visceral injury was 0·048 per cent (six of 12 444). These bowel injuries were reported in a gynaecological series. Four of six visceral lesions were recognized at the time of operation and repaired with no postoperative morbidity. The missed visceral lesions prompted laparotomy on the third and 11th postoperative day. There were no deaths. Vascular injury or gas embolism was not reported after open laparoscopy. Wound infection was noted in 44 of 12 444 (0·353 per cent) patients who had open laparoscopy and incisional hernia was noted in one of 869 (0·1 per cent).

Statistical analysis suggested a significant difference between closed and open laparoscopy when the total numbers of visceral and vascular injuries were considered together ($\chi^2 = 9{\cdot}41$, 1 d.f. $P = 0{\cdot}002$). While incidences of visceral injury at closed and open laparoscopy were not significantly different ($\chi^2 = 1{\cdot}70$), vascular lesions occurred significantly more frequently in patients having closed laparoscopy ($\chi^2 = 9{\cdot}37$, $P = 0{\cdot}002$). Comparison of mortality rates in patients having either closed or open laparoscopy did not reveal any significant difference ($\chi^2 = 0{\cdot}33$).

Discussion

Open laparoscopy was first described by Hasson in 1971[3]. In spite of the simplicity of the open technique, closed laparoscopy remains the preferred method of establishing a pneumoperitoneum[13]. In a survey in 1982 by the American Association of Gynecologic Laparoscopists[14], only 4 per cent of all laparoscopic procedures were done using open laparoscopy. Review of the literature revealed only 12 444 cases of open laparoscopy, compared with 489 335 cases of closed laparoscopy.

Prospective randomized studies of open *versus* closed establishment of pneumoperitoneum have not been performed. The available comparative studies involve retrospective analyses of relatively small numbers of patients[8,15]. Since the incidence of visceral and vascular injuries due to Veress needle or trocar insertion is low, a prospective study comparing open and closed laparoscopy would require excessive numbers of patients to allow statistically significant statements to be made. Analysis of the existing literature is, therefore, the only realistic way of comparing the complications of open and closed laparoscopy. Although the authors are aware of the fact that retrospective analyses tend toward under-reporting, it is assumed that under-reporting was a systematic error for both closed and open laparoscopy.

Surgeons who prefer the closed technique believe that the open method is time consuming and compromised by leakage of carbon dioxide during laparoscopy. However, in the authors' experience the insertion of the Hasson's trocar requires less than 5 min in most patients. Two comparative studies of open and closed laparoscopy have shown that the operative time of open laparoscopy is significantly shorter than that of closed laparoscopy[8,15]. Insufflation of the peritoneal cavity through the Veress needle is done with a low flow setting. In open laparoscopy, insufflation through a Hasson's trocar can be done with high flow because of its diameter of 10 mm; this permits time saving. Gas leakage along a Hasson's trocar is a potential disadvantage of open laparoscopy, but limiting the incision of the fascia and tight anchoring of the Hasson's trocar to the abdominal fascia prevent such leakage. In a situation of persistent gas leakage, a gauze swab inserted in the umbilical incision or an additional purse-string suture around the trocar usually solves the problem.

Closed laparoscopy in obese patients can be difficult for various reasons[16]. Lifting the abdominal wall before insertion of the Veress needle increases the distance between the abdominal fascia and the skin because the panniculus is usually loosely attached to the fascia. In addition, the peritoneum is pushed forward in front of the needle because of excessive preperitoneal fat. These problems are not encountered at open laparoscopy, because the fascia and the peritoneum are lifted individually and subsequently incised.

This study has shown that the incidence of vascular injury associated with closed laparoscopy is significantly greater than that of open laparoscopy. Vascular injury is recognized immediately in most cases and prompts emergency laparotomy to repair the lacerated vessel. Although various case reports of vascular lesions due to closed laparoscopy have appeared, the true incidence of such injuries is probably higher than reported in this study because a tendency exists not to publish complications[17–19]. It is evident that insertion of a blunt-tipped trocar under direct vision prevents lesions of blood vessels.

Visceral lesions are potentially more life-threatening than vascular lesions because they are commonly missed during laparoscopy and recognized only later when the patient develops symptoms of peritonitis. This explains the higher mortality rate of visceral lesions compared with that of vascular lesions. In only one series of open laparoscopies were visceral bowel injuries reported[11]. Careful incision of the peritoneum and choice of an access site remote from previous operative scars should minimize bowel lesions at open laparoscopy.

Gas embolism is a rare but often fatal complication of laparoscopy. It is caused by insufflating carbon dioxide into a blood vessel[20,21]. When the typical features of gas embolism, such as mill wheel heart murmur or a sudden increase of the end-tidal carbon dioxide, are absent, the problem can be confused easily with cardiac arrhythmia or myocardial infarction. The incidence of gas embolism in this review was 0·001 per cent after closed laparoscopy; open laparoscopy is highly unlikely to cause such embolism because the trocar through which the peritoneal cavity is insufflated is placed under direct vision.

Fascial closure of trocar sites remains controversial[22–24]. In the authors' study, the incidence of incisional hernia was 0·23 per cent using the closed technique. It is believed that inserting the trocar obliquely through the abdominal wall reduces herniation of the peritoneum or viscera. Closure of a 10-mm trocar site can be difficult technically, particularly in obese patients. In open laparoscopy, fascial closure is relatively simple because the stay sutures are used to close the fascia.

To prevent perforation of the viscera or blood vessels, disposable trocars with safety shields were developed in the late 1980s. The safety shield is supposed to shoot forward after the peritoneum has been penetrated. However, the shield can be held back for a considerable distance, particularly in cases of loose peritoneum[25]. This leaves the stylet of the trocar unprotected in the peritoneal cavity. In thin patients or when the abdominal wall is not elevated sufficiently, the unprotected stylet can easily cause visceral or vascular injury[18,26].

In recent years, disposable cannulas with transparent tips and either plastic rims or a mechanically triggered cutting blade for dissection of the abdominal wall have been developed[27]. During introduction of the trocar, the passage of the subsequent anatomical layers can be viewed with the laparoscope. Although these devices appear to be safer than trocars with a safety shield, discrimination of tissues during insertion through the abdominal wall is difficult, particularly the differentiation between peritoneum and bowel wall.

In summary, use of open establishment of pneumoperitoneum in laparoscopic surgery is advocated because it is safe, simple and can be performed with a reusable trocar which is cost-effective.

Acknowledgements

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Review

Blunt injury to the supra-aortic arteries

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Background Blunt trauma causing injury to the vessels of the aortic arch is uncommon but may be attended by serious consequences. Most surgeons will experience only an occasional case and will need to rely on published literature for guidance.

Methods A Medline search over 1986–1995 was carried out using the following keywords: brachiocephalic trunk, common carotid artery and subclavian artery; injury was used as a subheading.

Results and Conclusion After the aortic isthmus, the innominate is the most commonly injured artery in the chest. Whatever the site of an arterial lesion, however, angiography is the diagnostic test of choice. Some vascular lesions are relatively benign and may be managed without operation; this form of management may also be appropriate if there is severe associated neurological injury. Otherwise, operation using an approach and technique suited to the site of the injury is advocated.

Injury to the arch vessels caused by blunt trauma is rare yet may bear dire consequences. It is estimated that a thoracic vascular injury occurs in 4 per cent of blunt chest trauma, with a majority located at the aortic isthmus and a minority (between 5 and 20 per cent) involving the arch arteries[1–4]. Although a few surgical teams have reported a fairly wide experience of this type of injury[5–7], most trauma surgeons are likely to be confronted only occasionally with this difficult situation[8]. The challenge is twofold: establishing a rapid diagnosis in an often multiply-injured patient, and selecting an appropriate approach to repair a vessel that is located at the interface of the chest, neck and root of the upper extremity. This review, based on the authors' experience and a literature search, is intended to provide guidance to facilitate diagnosis and management.

Method

A Medline search scanning a decade (1986–1995) was undertaken, using brachiocephalic trunk, common carotid artery and subclavian artery as keywords, and injury as a subheading. The reference list of the English and French articles was checked to detect other articles that had not been listed. Articles dealing predominantly with penetrating injuries and those reporting treatment of injuries to the subclavian artery not requiring proximal arterial control or repair within the chest were discarded. A former review by Castagna and Nelson[8] (published in 1975) on 40 blunt injuries to the arch vessels was included. The distribution, association of lesions, operative treatment and outcome were established from three articles reporting series and from the review article (*Tables 1–3*)[5,8–10]. Other information (mechanism of injury, clinical presentation) and practical guidelines for rational management (operative exposure, cerebral protection and use of cardiopulmonary bypass) were also gathered or deduced from case reports and articles dealing with penetrating injuries.

Anatomical considerations

The supra-aortic arteries arise from the arch of the thoracic aorta. The arch curves around the right pulmonary artery and the left main bronchus and occupies, in a transverse plane, an oblique direction (*Fig. 1*). The origin of the innominate artery is anterior (close to the sternum) and to the right of the midline. The origin of the left subclavian artery is posterior (close to the vertebral column) and to the left of the midline.

The first centimetres of the arteries lie within the chest, and are well protected by strong musculoskeletal structures[11]. The subclavian arteries ascend in the neck for a short distance and then turn around the scalenus muscle and first rib to reach to the root of the upper extremities, whereas the carotid arteries ascend through the entire length of the neck. Anatomically, the upper limit of the arch arteries may be considered to correspond, more or less, to a horizontal line joining the origins of the vertebral arteries. From a surgical point of view it is appropriate to include also lesions slightly distal to this landmark if proximal control of the artery requires surgical entry to the chest[5,9].

Mechanisms and types of injury

Since the supra-aortic arteries are protected by strong musculoskeletal tissues, damaging a vessel usually requires a tremendous force. Not surprisingly, many patients present with multiple lesions, especially to the head and chest (*Table 1*)[5,6,8,12,13]. Traction and compression forces are responsible for most cases of aortic arch artery lesion. These forces are frequently produced by high velocity accidents with abrupt deceleration, such as head-on collisions or falls from a great height[3]. Displacement of the heart downwards and into the left chest during chest trauma strains the ascending aorta and the origin of the arch vessels, especially the innominate artery[14]. Hyperextension of the neck or rotation of the head may further strain the arterial wall beyond the limit of its elastic properties. Excessive traction of the shoulder puts an acute stretch on the subclavian artery at the thoracic

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Paper accepted 8 January 1997

Table 1 Associated injuries in patients with a supra-aortic artery injury

	Rosenberg *et al.*[5]	Castagna and Nelson[8]
No. of patients	30	36
Thoracic (non-vascular)	15 (50)	28 (78)
Orthopaedic	19 (63)	12 (33)
Closed head	14 (47)	10 (28)
Facial	14 (47)	4 (11)
Abdominal	7 (23)	3 (8)
Brachial plexus	6 (50)	6 (20)
Ascending aorta	n.a.	1 (3)
Aortic arch (or extension of tear into the arch)	n.a.	6 (17)
Aortic isthmus or descending aorta	4 (13)	5 (14)

Values in parentheses are percentages. n.a., Data not available

Table 2 Treatment of supra-aortic artery injuries

	Prêtre *et al.*[9]	Rosenberg *et al.*[5]	Castagna and Nelson[8]
No. of arterial lesions	13	29*	40‡
Non-operative treatment	1	5*	0
Ligation	2	4	1
Primary repair	5	20†	7
Graft interposition	5	0	28

*Three patients with four arterial lesions died before treatment; †not detailed; ‡two patients died before arterial repair and two repairs were unspecified

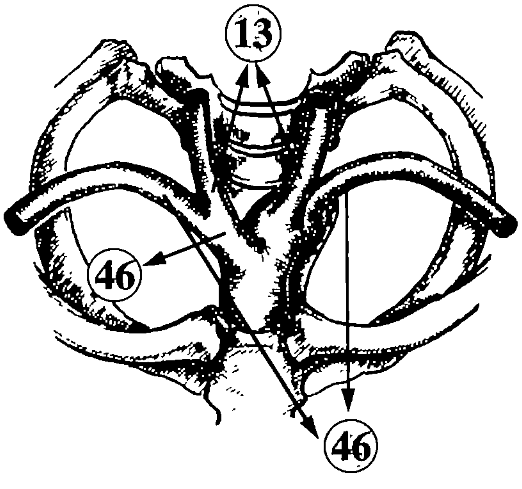

Fig. 1 Superior view of the thoracic inlet depicting the anatomical relationship of the supra-aortic arteries to the aortic arch The innominate artery is anterior, the left subclavian artery is posterior. The distribution of lesions (the aggregate from four series) is shown. *Table 4* details the distribution in each series

Table 3 Outcome of patients with a supra-aortic artery injury

	Prêtre *et al.*[9]	Rosenberg *et al.*[5]	Castagna and Nelson[8]
No of patients	12	30	36
Overall deaths*	1 (8)	3 (10)	6 (17)
Upper limb amputation†	2 (17)	6 (20)	n.a.
Brachial plexus damage	4 (33)	n.a.	n.a.

Values in parentheses are percentages. *Includes patients who died before surgical intervention; †all had disabling brachial plexus damage. n.a., Data not available

outlet, where it turns around the anterior scalenus muscle tendon and first rib[15-17]. The traction may simultaneously avulse the roots of the brachial plexus or lacerate its primary trunks. Lesions located at the proximal part of the brachial plexus are extremely grave and usually without hope of spontaneous recovery or possible repair (*Table 3*)[5,15,18]. Compression of the innominate artery between the sternum and thoracic vertebral column may occur during thoracic impact, such as a driver striking the steering wheel with his chest[19,20]. A direct injury to the artery has also been hypothesized in a few cases of damaged arch artery. Avulsion of the manubrium or internal luxation of the proximal head of the clavicle may impinge the innominate artery or the origin of the subclavian artery[11,21].

Depending on the plastic deformation created, traction or compression injuries produce tears of the intima, haematoma or disruption of the media, or complete transection of the artery. These injuries may remain quiescent, induce dissection, thrombosis, pseudoaneurysm of the artery or frank haemorrhage.

Distribution and association of lesions

Wide variations exist between published series regarding the relative rate of injury to each arch artery. *Fig. 1* and *Table 4* summarize the distribution of the lesions in three of the largest series and in a former review of the literature. It is generally acknowledged that, after the aortic isthmus, the innominate artery is the most commonly injured artery in the chest[3,7,8,10,22]. Because they share similar wounding mechanisms, arch vessel arteries may be damaged with other cardiovascular structures (*Table 1*). An association of injuries seems to exist with the thoracic aorta. In an institutional series of 66 patients with traumatic aortic isthmus rupture, Smith and Bansal[10] reported three patients with four lesions to the aortic arch arteries. In a review of the literature on blunt injury to the ascending aorta, it was found that three of 21 patients

Table 4 Distribution of supra-aortic artery injuries

	Smith and Bansal[10]	Prêtre *et al*[9]	Rosenberg *et al.*[5]	Castagna and Nelson[8]
Innominate artery	5	2	17	22
Right common carotid artery	0	1	8	0
Left common carotid artery	4	0		0
Right subclavian artery	3	5	8	9
Left subclavian artery	7	5		9

Reference 8 is a review of the literature The overall distribution of lesions is shown in *Fig. 1* with such injury had a concomitant lesion to the arch arteries[23]. Although a relationship between a cardiac and supra-aortic artery injury is impossible to establish in the absence of large series, case reports on blunt cardiac trauma sporadically mention a concomitant lesion to the arch artery[20,24].

Clinical presentation

In contrast to penetrating wounds, a minority of blunt arch vessel injuries produce critical physiological derangement such as massive haemorrhage, cardiac tamponade, acute limb or brain ischaemia, or acute compression of the airway tract or brachial plexus[3,5,25–27]. Massive haemorrhage is uncommon (because the haematoma usually remains contained in periadventitial tissues) unless blood enters a pleural cavity, as may occur with rupture of the proximal part of the left subclavian artery[26–28]. Cardiac tamponade may complicate avulsion of the origin of the innominate artery when the tear extends for a few millimetres on to the ascending aorta, across the pericardial reflection. Coma or hemispheric stroke may occur with acute occlusion of the common carotid artery[26,27]. Dissection, a common traumatic lesion of the extracranial carotid arteries, may progress distally over a few hours, reach and occlude the internal carotid artery, and produce neurological deficit after a lucid period[13,29–31]. Prolonged compression of the brachial plexus by a tense haematoma may lead to permanent damage[6]. In these critical situations, a favourable outcome can only be expected after swift diagnosis, delineation of the injury and correction of the insult, a task that may prove extremely challenging when other injuries co-exist.

Fortunately, the majority of arch vessel injuries offer a less dramatic picture and present mostly with clinical features of an arterial occlusion. Decreased or absent radial or carotid pulses, a palpable supraclavicular mass or haematoma (especially if pulsatile and growing) at the base of the neck, and a supraclavicular bruit on auscultation are signs of a vascular injury[3,5,8,17,25–27]. Signs of diminished perfusion of the upper extremity may be present (coldness, prolonged capillary refill) but, thanks to the efficient collateral network of the neck and shoulder, critical ischaemia is rare even in cases of major destruction of the shoulder girdle[5,16,26,32]. Sampson *et al.*[32] reported only one case of critical ischaemia in 11 patients with scapulothoracic dissociation (one of the most devastating injuries to the shoulder) and this patient had an associated traumatic occlusion of the brachial artery. Full-thickness laceration or rupture of the artery may produce a haematoma that evolves into a pseudoaneurysm. The pseudoaneurysm may grow and compress neighbouring structures or release emboli[6,8,13,31]. Dysphagia, superior vena cava syndrome, recurrent laryngeal nerve palsy, and cerebral or digital embolization have occasionally been seen as the presenting sign of a traumatic pseudoaneurysm of an arch artery[6,8]. Finally, a significant number of arch vessel lesions are discovered incidentally, mostly during angiography of the thoracic aorta[6,9,20,33].

Radiological diagnosis

The sensitivity of supine anteroposterior chest radiography in the detection of a thoracic arterial injury is 90 per cent, mostly through abnormal widening of the superior mediastinum and the presence of extrapleural haematoma[3,5,34,35]. These signs, however, have a low (10–15 per cent) positive predictive value for an arterial injury, and radiographs may be normal in as many as 7 per cent of patients with thoracic artery damage[36,37]. Fracture of the first ribs has been recognized as a hallmark of severe trauma and, in the 1970s, it was thought that this sign was associated with an increased incidence of thoracic vascular injury[38–40]. Many reports later appeared in the literature: a few confirmed the association[40,41] but the majority rejected it[42–45]. In an extensive review of this topic, Poole[11] found that no more than 3–5 per cent of patients with first rib fractures had an injury to the supra-aortic trunks or thoracic aorta (and virtually all of them had a widened mediastinum) and concluded that, with the exception of direct injury to the subclavian artery, there was no association between these fractures and a thoracic vascular injury.

Angiography, the role of which is now frequently challenged by other diagnostic methods in the evaluation of many arterial segments, remains undisputed for assessment of the arch arteries[3,6,9,13,19,34,46]. It elucidates the nature of the arterial lesion, specifies the anatomy of the arch arteries with respect to possible anatomical variation, and assesses the entire thoracic aorta to detect associated vascular injuries. In cases of injury to the left subclavian artery, a balloon can be positioned and inflated in the proximal portion of the artery to provide control[9,18]. Transthoracic (including suprasternal views) and transoesophageal echocardiography with multiplanar views, so often proposed as an exclusive screening or diagnostic tool for vascular injuries in patients with chest trauma, often fail to delineate the arch vessels (especially the origin of the innominate artery, the second most commonly injured artery in the chest) and may miss an injury[3,10,46,48]. Conventional computed tomography of the chest rely mostly on indirect signs of vascular injury (the presence of a paravascular haematoma) to detect a lesion of the arch arteries[3,49,50]. Helical computed tomography might be suitable for screening a thoracic vascular injury (including the arch vessel), but its precise accuracy and role in evaluating chest trauma remain to be defined[51]. Magnetic resonance imaging, while as informative as angiography, requires a heavy infrastructure and long acquisition times during which close surveillance of the patient is impossible. This limits dramatically the suitability of this form of examination in acutely injured patients.

Non-operative management

A non-operative approach has been proposed for benign arterial lesions and for stable arterial lesions that have produced or are associated with severe neurological injuries (*Table 2*)[32,52,53]. It has been established that limited intimal flaps and haematoma producing only lumen irregularities can be watched safely for a period of time[52]. Pseudoaneurysms (even small ones), however, should be repaired because of their potential associated complications; embolization or increasing size with delayed rupture may induce devastating consequences if the emboli occlude an artery of the brain or haemorrhage occurs into a pleural cavity[31,54]. Endovascular grafts have been successfully inserted percutaneously in penetrating injuries of the subclavian or axillary arteries to exclude small pseudoaneurysms or occlude an arteriovenous fistula[55,56]. It is conceivable that intimal flaps producing significant stenosis and most pseudoaneurysms will be approached by this emerging technique in the years to come[55]. Severe neurological deficit (coma or complete hemiplegia) produced by acute occlusion of a carotid artery is usually a consequence of a brain infarction, so revascularization, even the speediest, cannot restore function. Neurological improvement has been claimed following vascular repair in patients with hemiplegia due to penetrating injury of the carotid artery[57,58]. This benefit, however, has been disputed as it may well be a result of natural evolution rather than surgery; other authors have reported spontaneous improvement with supportive measures alone[34].

Damage to the carotid artery after blunt trauma is often widespread[30,31,54]. In a multicentre analysis of 60 blunt carotid artery injuries, Cogbill *et al.*[29] noted that frank arterial rupture was uniformly fatal from haemorrhage or brain ischaemia, that arterial thrombosis or dissection often extended along the entire length of the carotid axis and that neither was amenable to surgery. In this review, thrombosis carried a poor prognosis: a 40 per cent mortality rate with an additional 30 per cent associated with severe neurological deficit. Dissection has a more favourable outcome. Mokri and co-workers[59] reported an 11 per cent mortality rate with an additional 11 per cent neurological disability rate in 18 patients with internal carotid artery dissection. Anticoagulation to prevent formation or propagation of thrombus in the dissected artery is classically recommended, although its usefulness in preventing delayed occlusion of the internal carotid artery and further neurological deficit has never been clearly demonstrated. In non-randomized retrospective studies, however, a benefit of anticoagulation has regularly been claimed and its use seems to be warranted unless there are specific contraindications[12,13,29,30,34]. At present, it is acknowledged that resection and grafting of a carotid artery is indicated for thrombosis or dissection limited to the common carotid vessel, and for accessible pseudoaneurysms.

Some lesions of the subclavian artery are associated with complete brachial plexus palsy[15–17]. Spontaneous recovery is unlikely if the palsy results from avulsion of the roots or primary trunks of the plexus (*Table 3*)[17] and revascularization seems futile for a limb that will remain flail. In a similar setting of patients (those presenting a brachial plexus palsy and a distal subclavian artery rupture in the case of scapulothoracic dissociation), Sampson and co-workers[32] deliberately chose not to operate the occluded artery if critical ischaemia or active haemorrhage was not present. Secondary bleeding or worsening of ischaemia did not occur in the five patients so treated.

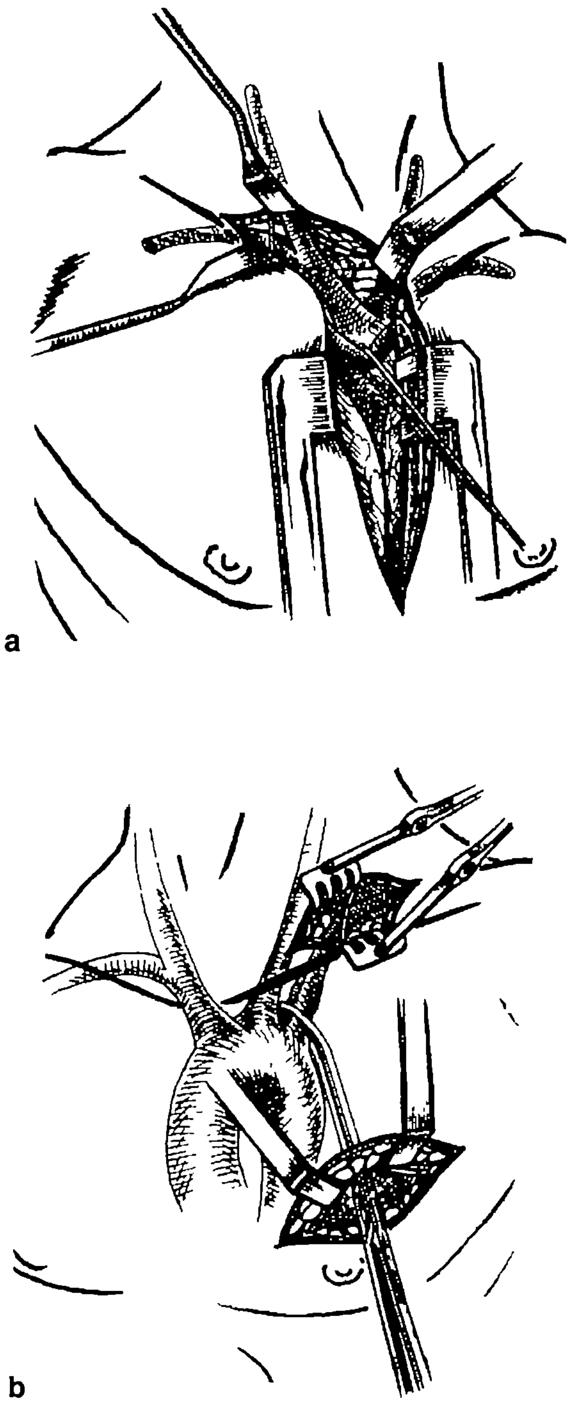

Fig. 2 a Surgical approach to the innominate and left common carotid artery is achieved by sternotomy with cervical or supraclavicular extension of the incision. b Surgical approach to the left subclavian artery can be achieved by a combined anterolateral thoracotomy in the third intercostal space for proximal cross-clamping and a left supraclavicular incision for repair

Operative management

Proximal lesions of the arch arteries require entry to the thorax. Median sternotomy with supraclavicular or cervical extension of the incision provides excellent exposure of the anteriorly positioned arch arteries: the innominate, the right subclavian, and the right and left common carotid arteries (*Fig. 2*). Because of its posterior location, the left subclavian artery is better accessed through a left thoracotomy[7,9,26,34]. A trap-door incision, which elevates and retracts laterally the first three ribs, also allows exposure of the intrathoracic portion of the left subclavian artery[60]. The aperture is limited, however, and cannot afford safe repair of injuries of the origin of the artery and those extending on to the aorta. A posterolateral thoracotomy in the third or fourth intercostal space is more appropriate for repair of the intrathoracic part of the left subclavian artery. Distal control of the artery, if the perivascular haematoma extends toward the neck, can be achieved through this route by insertion of an inflatable balloon or by extending the incision posteriorly between the scapula and the spine. This allows elevation of the shoulder off the chest wall, exposure of the first rib over which lies the subclavian artery, and placement of a vascular clamp[5,61]. Finally, anterior thoracotomy in the third or fourth intercostal space offers emergency proximal control of the innominate or the right or left subclavian arteries in cases of massive bleeding in the pleural cavity, a very uncommon situation in blunt trauma[34].

More distal lesions of the subclavian arteries (close to the vertebral artery origin) can be approached by a supraclavicular incision[6,26,34]. The entire chest should be prepared, in case proximal control is difficult and requires opening of the thorax. Sternotomy permits rapid cross-clamping of the innominate or proximal right subclavian artery, and left anterior thoracotomy in the third intercostal space permits crossclamping of the left subclavian artery (*Fig. 2*). An intravascular balloon can also be inserted during angiography in the intrathoracic portion of the left subclavian artery and inflated to provide proximal control and to avoid an additional thoracic incision[9,18]. More distal exposure of the subclavian artery is achieved by extending the incision along the deltopectoral groove. Some surgeons preserve the clavicle, some divide it and reconstitute it using orthopaedic techniques after vascular repair, and others simply resect its middle third[6,26,27]. Although claviculectomy has been reported to induce only limited morbidity, a preservative approach may be more appropriate when dealing with a fairly straightforward vascular lesion in a young patient[9,18,34].

Operation

Operation centres on three principal options: primary repair, interposition of a graft and ligation (*Table 2*). Primary repair is frequently not possible because the arterial lesion extends over a few centimetres and even sacrifice of collateral branches does not provide sufficient length to allow a direct anastomosis[27]. Direct implantation of the left subclavian artery into the left common carotid artery has been performed after the traumatized origin was oversewn[8]. Interposition grafts, mainly autologous saphenous vein or prosthetic grafts, are associated with excellent patency rates and extremely low infective complications in this context[5,6,34] and offer numerous possibilities for repair. The approach to a lesion located at the origin of the innominate or left common carotid artery requires care; tangential application of a clamp on the aortic arch to occlude the injured artery may be dangerous and is inadvisable[7,19]. Selective clamping of a single arch artery may be difficult to achieve because the vessels lie closely together. In up to 10 per cent of the population anatomical variations of the arch arteries exist, the most dangerous being the origin of the left common carotid artery from the innominate artery, which precludes occlusion of this common trunk[7,19,62]. For these reasons, it is appropriate to approach a haematoma at the origin of these arteries by first inserting a prosthetic graft on the ascending aorta[19,22]. The graft is then connected to the artery distal to the lesion and, after flow has been restored in this artery, tangential clamping of the aortic arch and oversewing of the origin of the injured artery is performed (*Fig 3*). Even if the clamp partially interferes with perfusion of the left common carotid artery,

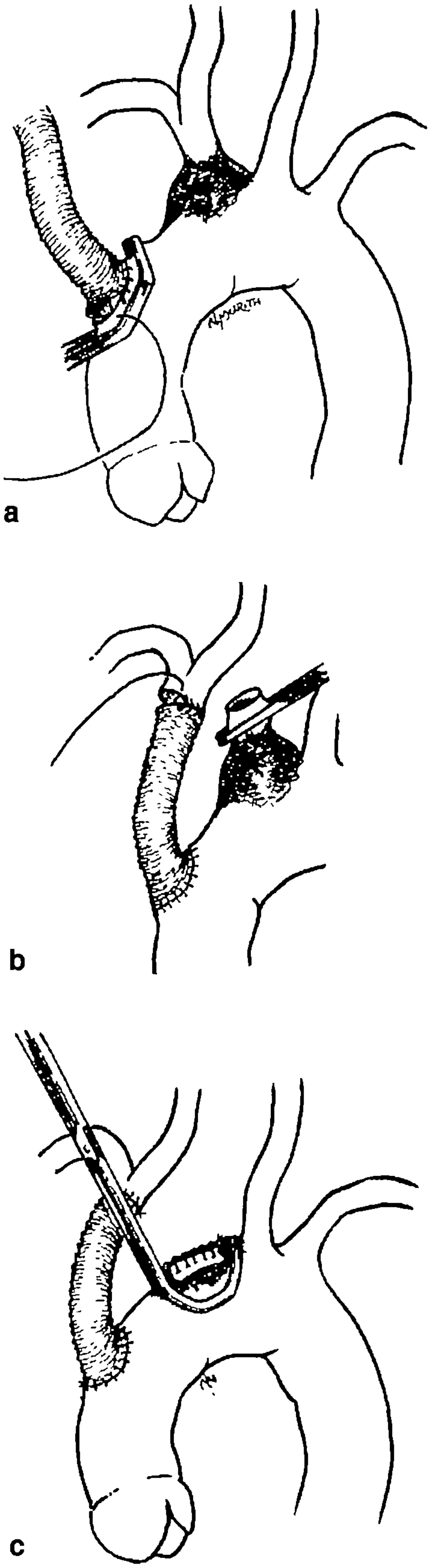

Fig. 3 Surgical repair of a lesion at the origin of the innominate artery is safely performed by first inserting a prosthesis on the ascending aorta (a), connecting it to the injured artery (b) and, after the artery is perfused, by clamping and oversewing the origin of the vessel (c)

ischaemia of the brain should not occur as there is perfusion in the contralateral carotid artery.

Lesions at the origin of the left subclavian artery may be approached directly, with the surgical trauma and anaesthetic teams prepared to cross-clamp the descending aorta. This should be done ideally after blood pressure and volume are corrected, unless active bleeding dictates immediate control. Aortic cross-clamp time should be as short as possible to prevent ischaemic damage to the abdominal viscera and the spinal cord[63]. Ligation of an arch artery is recommended in desperate conditions when active bleeding exists and concomitant injuries need immediate attention, or when severe and hopeless neurological deficit exists[6,9,18,29,34].

Resort to passive shunting or active perfusion of the carotid arteries during cross-clamping has led to considerable debate and, to some extent, reflects the philosophy of the surgical team involved. In Castagna and Nelson's review[8], extracorporeal circulation with cannulation and perfusion of the carotid artery was used in seven and an indwelling shunt in three of 21 patients with repair of the innominate or common carotid artery. On the other hand, the Ben-Taub Hospital group[7,64], with its unparalleled experience of vascular trauma, never uses any form of circulatory support and does not report increased ischaemic damage. Cross-clamping the origin of a single supra-aortic trunk is probably safe if blood pressure and oxygen saturation are normal[7,19,60]. A pressure in the carotid artery distal to the cross-clamp of more than 50 mmHg is deemed adequate in this setting and may be measured directly if doubts exist on direct palpation of the artery beyond the clamp[5,65]. Rosenberg and co-workers[5] did not find a pressure drop below this critical value during innominate or carotid artery cross-clamping in their patients, and did not experience neurological deficit related to the repair without arterial shunting. The availability of extracorporeal circulation is not a luxury in cases of avulsion of the origin of a supra-aortic trunk. The tear may extend to the adjacent aorta and prove difficult to repair under normal blood pressure[8,19]. Fine control of the blood pressure (and hence of the stress on the wall of the aorta), moderate hypothermia to protect the brain and reinfusion of aspirated blood are the advantages of extracorporeal circulation. The need for anticoagulant, even if heparin-bonded circuits are used, and profound haemodilution are the major drawbacks, especially for multiply-injured patients who may have many potential sources of bleeding.

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Analysis of randomized controlled trials in laparoscopic surgery

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Background Randomized controlled studies of surgical procedures are difficult, but can be done to acceptable standards. There are few published objective assessments of such trials.

Methods The original articles that involved a randomized controlled trial including at least one laparoscopic procedure were reviewed and evaluated with special interest in their methodology. An assessment form containing 11 generic questions and three additional criteria (assessment of quality of life, cost analysis and laparoscopic experience required) was used. Forty trials were retrieved including 12 on cholecystectomy, 12 on hernia repair and 12 on appendicectomy. Each trial was scored by two assessors.

Results The agreement among the two independent assessors was very good. Six of the trials were well conducted but 22 had a poor score. The trials on cholecystectomy were scored the best in contrast to those on hernia repair or appendicectomy. Few trials provided an adequate prospective calculation of the sample size, an unbiased assessment of endpoints, evaluation of the quality of life and a study of the economic aspects.

Conclusion Readers should be cautious when interpreting the results of some of these trials and their impact on daily surgical practice.

There is unanimous agreement that a randomized controlled trial is the best available method for evaluating alternative therapies including surgical procedures. Contrary to medical trials, surgical randomized controlled trials involve particular difficulties such as the feasibility of blinding, the influence of the surgeon's skill and experience, and the practitioner's or patient's preferences[1–4]. Nevertheless, it has been shown that 40 per cent of surgical procedures could be evaluated by a randomized controlled trial[5]. With the advent of minimally invasive surgery in the late 1980s, it was suggested that a randomized controlled trial was needed to evaluate laparoscopic cholecystectomy. Contrary to the opinion of some authors[6], several teams initiated randomized controlled trials in the early 1990s to compare laparoscopic with open procedures.

The randomized controlled trial as a 'gold standard'[7] should be well designed and well conducted. Flaws in the design or analysis of randomized controlled trials will hinder interpretation of their relevance to daily practice, particularly in this type of surgery where there is large demand from practitioners, patients and even the media. The assessment of the quality of randomized controlled trials is not new[8] but the study of methodological standards in surgical randomized controlled trials is rare. To the authors' knowledge, there are only three papers that have focused on this problem[9–11]. In the latter study, 16 of 346 randomized controlled trials concerned aspects of laparoscopic surgery.

The aim of this study was to review the methodology of randomized controlled trials in laparoscopic surgery and to perform critical analysis of these trials. This study was an assessment of randomized controlled trials as they have been published.

Methods

A computerized search technique (MEDLINE and Current Contents) together with a manual search was used to identify original articles published between January 1990 and November 1996 that reported a randomized controlled trial comparing two or more surgical procedures including at least one laparoscopic procedure, or a laparoscopic technique with a non-surgical treatment. Experimental or non-randomized studies as well as editorials, letters, abstracts, reviews and redundant articles were excluded.

Criteria of assessment

Assessment form. This was derived from, and was a modification of, a published assessment form[11]. It recorded the name of authors and the journal in which the study was published, the nature and number of treatment groups, and the number of patients included. The form also contained 11 questions which were chosen because of their generic nature from the reader's perspective (*Table 1*)

All the questions required one of three responses: 0, criterion not reported; 1, criterion reported but inadequate; or 2, criterion reported and adequate. Scores for each question were summed to give a total score for each trial. A maximum total score of 22 was possible, which represented an 'ideal' randomized controlled trial according to these criteria. The assessment form also contained an area for comments.

Other assessment criteria. Supplementary criteria requiring a positive or negative response were assessment of quality of life outcomes, cost analysis of the alternative procedures, and a statement on the experience of participating surgeons in laparoscopic surgery before undertaking the trial.

Method of assessment

The assessors who participated in the evaluation of the trials comprised three surgeons and one statistician. Each publication was reviewed by two assessors independently and the interassessor variations were noted. The measurement of agreement among assessors was studied by calculating the crude proportion of concordant observations. Weighted Kappa (κ) statistics were used for evaluating interassessor agreement[12,13].

The agreement was quoted according to the value of weighted κ as moderate (less than 0·60), good (0·60–0·79), or very good (0·80–1·00)[13]. The final assessments were based both on the initial agreement and the consensus after further review. The proportion of trials that were assigned a score of 2 for each of the 11 items and the total score for each trial were calculated.

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Table 1 Topics about which questions on the assessment form recorded information

1	A stated aim
2	An adequate control group (a group receiving a current 'gold-standard' therapy)
3	An account of the selection process (information about the criteria of inclusion and exclusion)
4	A prospective definition of sample size (information on the size of detectable differences of interest, the declared probability of type I error and estimates of power)
5	A description of the randomization technique (specific information about the technique used for allocating operations)
6	Demonstration of baseline equivalence (description of the patients under study and the risk factors that might confound interpretation of the results)
7	Definition of the study endpoints (unambiguous explanation of the criteria used to evaluate the presence or absence of the main outcome events including the complications that occur after any operation)
8	An unbiased assessment of the study endpoints (whether the assessors of the main outcome were aware of the type of operation that each patient was receiving)
9	A description of the operations (other investigators should be able to reproduce accurately the procedure on the basis of this account)
10	Adequate postoperative follow-up (sufficiently long to allow documentation of adverse events) For the randomized controlled trials on hernia repair the follow-up was considered adequate if the authors stated clearly that the study focused only on the early results
11	Adequate statistical analysis (whether the statistics were in accordance with the type of the study, and the confidence intervals or relative risks were calculated)

The trials were placed according to their scores in category A (score 20–22), category B (17–19), and category C (16 or less).

Results

Description of trials

Forty original articles involving a randomized controlled trial on laparoscopic surgery have been retrieved (references of these articles can be obtained from K.S.). They have been published in *Br J Surg* (seven), *Lancet* (five), *Surgery* (four), *Ann Surg* (three), *Chirurg* (three), *J Am Coll Surg* (three), *Surg Endosc* (three), *Am J Surg* (two), *Ann Chir* (two), *World J Surg* (two), *Arch Surg* (one), *BMJ* (one), *South Med J* (one), *J Chir* (*Paris*) (one), *Int J Colorectal Dis* (one) and *Surg Laparosc Endosc* (one). All but five randomized controlled trials compared laparoscopic with open procedures. There were 12 trials on cholecystectomy, 12 on inguinal hernia repair, 12 on appendicectomy, one evaluating two techniques of laparoscopic control of short gastric vessels (by clipping or ultrasonic coagulation) during Nissen fundoplication, one evaluating laparoscopic repair of perforated peptic ulcer (four arms: laparoscopic suture and sutureless technique *versus* open suture and sutureless technique). One trial compared laparoscopic and open colorectal resections and one compared several techniques of port wound closure. Thirty-three trials studied several outcomes and seven focused on postoperative pulmonary function and/or pain and/or hormonal response or oral feeding.

The median (range) number of patients included was 80 (20–310) in the trials on cholecystectomy, 96 (61–181) for those on inguinal hernia repair, 70 (37–253) for appendicectomy, 31 in the randomized controlled trial on Nissen fundoplication, 103 in the trial on perforated ulcer repair, 30 in the trial on colorectal surgery, and 95 port sites in 32 patients in the trial on port wound closure.

Assessment of trial methods

The overall crude agreement rate among the assessors was 93 per cent. The agreement was very good with $\kappa = 0{\cdot}92$.

Six trials were placed in category A, 12 in category B and 22 in category C (*Tables 2* and *3*). The numbers of randomized controlled trials that provided adequate details (scored 2) for each of the 11 items are shown in *Table 4*. The majority of the trials provided a clear aim,

Table 2 Scores of the trials related to the procedure studied

	Category		
Procedure	A	B	C
Cholecystectomy	5	3	4
Hernia repair	1	5	6
Appendicectomy	0	3	9
Others	0	1	3
Total	6	12	22

Category A: score 20–22, Category B: 17–19; Category C: 16 or less

Table 3 Scores of the trials related to the journals in which they were published

	Category		
Journal	A	B	C
Br J Surg	2	2	3
Lancet	2	2	1
Surgery	1	1	2
BMJ	1	0	0
Others	0	7	16

Table 4 Number of trials that provided adequate details for each of the 11 items

Criterion	No. of trials
Aim	34 (85)
Control group	33 (82)
Selection process	35 (88)
Prospective evaluation of the sample size	10 (25)
Randomization technique	20 (50)
Baseline equivalence	23 (58)
Study endpoints	35 (88)
Unbiased assessment	6 (15)
Description of the operations	32 (80)
Postoperative follow-up	31 (78)
Statistics	28 (70)

Values in parentheses are percentages

with adequate control group, inclusion criteria, endpoints, description of the operations, postoperative follow-up and statistical analysis. Half of the trials gave a clear and adequate statement on the randomization technique, and the baseline equivalence. Few trials provided a prospective adequate calculation of the sample size and an unbiased assessment of the study endpoints.

Five trials assessed quality of life using established scores[14–16]. Eight trials studied the economic aspects (cost-effectiveness) of the procedures. After exclusion of seven trials that focused on a particular postoperative endpoint, quality of life and cost-effectiveness were assessed in five and eight of 33 trials respectively. Twelve of the 35 trials comparing laparoscopic with open procedures gave a statement on the required experience in laparoscopic surgery before participation in the trial. The number of laparoscopic procedures required varied from five to 50.

Evaluation for each procedure

Cholecystectomy. Nine trials compared the laparoscopic approach with laparotomy (minilaparotomy or classical Kocher incision) and three compared two laparoscopic procedures or instruments ('French' *versus* 'American' techniques, conventional *versus* wall lift techniques, and bipolar *versus* monopolar scissors). Among the 12 trials, seven studied several postoperative outcomes, three focused on postoperative pulmonary function (including one trial studying both pulmonary function and postoperative pain), and two reported postoperative stress hormone responses. One trial was published in three different journals, reporting the immediate postoperative outcome, pulmonary function and postoperative pain, and finally the 1-year outcome.

The trials on cholecystectomy were the best scored trials (eight placed in categories A or B). They represent the majority of the trials where the sample size has been calculated prospectively with respect to hospital stay and/or convalescence and/or general health status (six trials). When recorded, the required number of previous laparoscopic cholecystectomy procedures for participation in the trial was ten in one trial and more than 30 in five trials.

Inguinal hernia repair. The therapeutic arms varied greatly between the trials. Seven trials compared the transabdominal preperitoneal laparoscopic technique with the Shouldice repair (two), the nylon darn technique (three), the tension-free mesh repair (one) and various open techniques (one). Two trials compared the totally extraperitoneal laparoscopic technique with the Shouldice repair. One trial had three arms (transabdominal, totally extraperitoneal and Shouldice repairs). One trial compared the extraperitoneal repair with the Stoppa technique. Finally, one trial compared the onlay technique with Bassini or Mac Vay repairs.

One trial was placed in category A, five in category B and six in category C. The sample size had been calculated in three trials. This calculation was done in one trial with respect to a 50 per cent reduction in use of analgesics. All of the trials reported preliminary results (thus excluding recurrence). Two trials assessed quality of life and three the cost-effectiveness of the procedures. The required number of previous laparoscopic hernia repairs was low in two trials (five and ten) and more than 20 in two trials.

Appendicectomy. Two trials concerned diagnostic laparoscopy for suspected appendicitis. Among the ten trials evaluating therapeutic laparoscopy, nine trials had two arms and one had three arms (open, laparoscopy using a stapler device and laparoscopy using a catgut ligature).

None of the trials of appendicectomy was placed in category A and three-quarters were in category C. The median number of patients (70) was the lowest and a prospective calculation of the sample size was done in only one trial. The required laparoscopic experience was stated in two trials (15 procedures in one and 'skilled surgeons' in the other). Thus the randomized controlled trials on appendicectomy represent the poorest trials in this study.

Discussion

The recent explosion in minimally invasive techniques is one of the major features of contemporary surgical practice. Fortunately, several teams have progressed from descriptive and anecdotal reports to prospective or randomized controlled trials allowing progression 'from a perspective of what can be done to what should be done, or what is effective and of optimal benefit to the patient'[17]. A randomized controlled trial remains the best method to evaluate objectively a new and often controversial technique. There are numerous examples of operations that had initial success but which were rejected after well conducted randomized controlled trials[18]. A formal randomized controlled trial appears mandatory to allow a valid assessment of a new treatment such as laparoscopic surgery. Such trials should be well designed and well conducted.

The results of this study show clearly that more than half of the trials were poorly constructed or at least poorly reported. The observation that many randomized controlled trials fail to reach their full potential because of defective design has been reported previously by several authors regarding medical[19,20] or surgical[9–11] trials.

These results are similar to those reported in other studies evaluating randomized controlled trials in conventional surgery[9–11], suggesting that the quality of randomized controlled trials has not improved with the advent of minimally invasive surgery. One study has noted the lack of improvement in the quality of randomized controlled trials in conventional surgery between 1980 and 1990[9]. Moreover, Hall *et al.*[11] concluded that less than 50 per cent of the 364 trials evaluated made comment about an unbiased assessment of outcome, gave an adequate description of the randomization technique or provided a prospective estimate of the sample size; quality of life and economic factors were studied in 6 and 2 per cent of the trials respectively. Solomon *et al.*[10] using the global Chalmers' qualitative score[8] also concluded that the proportion of surgical trials and standards of surgical trials were low.

Two features of the present study deserve comment. First, the interassessor agreement was very good probably because the questions required three precise types of response. Second, the assessment of previous laparoscopic experience of surgeons participating in the trials was added to the classical methodological standards (including analyses of quality of life and cost-effectiveness). The learning curve for laparoscopic procedures is a recognized contributory factor in complications. However, the experience of participating surgeons was stated in less than half of the trials and in some trials the participating surgeons had performed only ten or fewer procedures before entering into the trial. These numbers are clearly insufficient[21–23] and may be a potential source of bias. It is also important to note in the present study that two of the major outcomes after laparoscopic surgery (quality of life and cost-effectiveness) were assessed in only five and eight of the 40 trials. This is surprising because one of the theoretical advantages of this type of surgery is its minimally invasive aspect, and the economic consequences of laparoscopic access are controversial.

The quality of the trials on hernia repair and appendicectomy was moderate or poor. Of particular note was the absence of prospective calculation of the sample size (and thus a possible inadequate power or type II error[24]) and unbiased assessment of outcome, in addition to the points highlighted above. These deficiencies could hinder interpretation of their relevance for daily practice and should lead readers to be cautious when interpreting and applying the results[25]. For example, in the field of hernia repair only five of 12 trials compared a laparoscopic technique with the Shouldice repair which is probably the current best conventional method[26], and only one trial compared the laparoscopic technique with the tension-free mesh repair.

Several randomized controlled trials are needed to compare, for example, endoscopic cholangiopancreatography *versus* laparoscopic surgery of the common bile duct, laparoscopic *versus* open fundoplication and laparoscopic complete *versus* posterior fundoplication, laparoscopic myotomy *versus* pneumatic dilatations, transabdominal *versus* preperitoneal laparoscopic herniorrhaphy, and laparoscopic *versus* open colorectal surgery (particularly concerning the oncological aspects). These trials should be properly designed and reported, like the majority of published trials on cholecystectomy. Future studies should pay a special interest to quality of life evaluation[27,28] and analysis of cost-effectiveness[29,30] in times when health care budgets are ever decreasing[31].

Obviously, questions involving surgical operations may not need to be answered by randomized controlled trials[5] but may be studied by well designed prospective studies[32,33]. However, well conducted prospective trials (randomized whenever possible) are the best way to evaluate new procedures. These trials may involve an additional cost but it has been clearly demonstrated that they are in fact a good investment[34].

Generally, a greater emphasis in surgical education on critical evaluation and research methodology is important. The referees used by journals should be more critical with respect to the quality of reporting of randomized trials. It was not surprising to note in this study that the majority of the best scored trials had been published in well ranked journals. Recently, the Standards of Reporting Trials (SORT) group from North America published the 'CONSORT' statement to improve the quality of reporting of randomized controlled trials[35]. The editors of *JAMA* will incorporate this statement and its requirements in their instructions to authors from January 1997[36]. It is hoped that this step forward will help to promote unbiased surgical research.

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Abdominal wall hernia in autosomal dominant polycystic kidney disease

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Background Autosomal dominant polycystic kidney disease (ADPKD) is a common cause of renal impairment with a number of well recognized extrarenal associations. A high incidence of abdominal wall hernia was noted in patients with ADPKD.

Methods A retrospective review of the notes of all patients with ADPKD on the South Wales renal replacement therapy database was performed. These patients were compared with age- and sex-matched patients with renal failure but without ADPKD and with general surgical patients.

Results The prevalence of hernia in patients with ADPKD was 38 of 85 (45 per cent) compared with seven of 85 (8 per cent) for other forms of renal failure and three of 85 (4 per cent) for general surgical controls ($P < 0.001$). There were significantly greater numbers of inguinal ($P < 0.001$), incisional ($P = 0.019$) and paraumbilical ($P = 0.007$) hernias in patients with ADPKD compared with the other two groups.

Conclusion These results show a significantly greater incidence of hernia, which could be an additional manifestation of the underlying defect in extracellular matrix production identified in patients with ADPKD.

Autosomal dominant polycystic kidney disease (ADPKD) is a relatively common renal condition with an incidence of between 1 per 400 and 1 per 1000 of the population[1]. It represents one of the most common indications for renal replacement therapy.

It is well documented that patients receiving continuous ambulatory peritoneal dialysis (CAPD) are at increased risk for the development of abdominal wall hernia. The authors have observed that patients with ADPKD have a higher incidence of herniation, not only during CAPD but also before the diagnosis of their renal disease, while on haemodialysis and after successful transplantation.

To confirm this observation, the notes of all patients with ADPKD on a renal replacement therapy database were reviewed and compared with data from patients with renal failure of other cause and a control group of general surgical patients.

Patients and methods

The South Wales renal replacement therapy database contains details of all patients with end-stage renal disease including those on haemodialysis and CAPD as well as patients after successful transplantation. Two control groups were assessed for comparison consisting of age- and sex-matched patients with renal failure without ADPKD and a group of general surgical patients. The patients with ADPKD and non-ADPKD renal failure were also matched in terms of numbers on each form of replacement therapy and duration of treatment. The general surgical patients had conditions other than hernia.

The notes of these patients were reviewed and details of age and sex were recorded together with location, mode of presentation, age at diagnosis and subsequent management of any hernia. A note was also made of established predisposing factors for herniation. In addition, the form of renal replacement therapy and the duration of treatment were also noted, as was the type of renal disease for all patients with renal failure.

Results were analysed by the Yates', χ^2 and Fisher exact tests, $P < 0.05$ was considered to be significant.

Results

Patient demographics are summarized in *Table 1*. The number of abdominal wall hernias including inguinal, incisional and paraumbilical are documented in *Table 2*. Forty-one hernias were noted in 38 patients with ADPKD (three had bilateral inguinal hernias) compared with seven

Table 1 Patient demographics

	ADPKD	Non-ADPKD	General surgical
No.	85	85	85
Sex ratio (M:F)	39:46	39:46	39:46
Mean (range) age (years)	59 (23–74)	57 (29–75)	56 (21–83)
Form of renal therapy			
CAPD	14	14	—
Haemodialysis	11	11	—
Transplantation	60	60	—

ADPKD, autosomal dominant polycystic kidney disease; CAPD, continuous ambulatory peritoneal dialysis

Table 2 Prevalence of hernia

	ADPKD	Non-ADPKD	General surgical
Patients with hernia	38	7	3
Prevalence of hernia (%)	45	8	4
Type of hernia			
Inguinal	25	5	3
Incisional	6	1	0
Paraumbilical	7	1	0

ADPKD, autosomal dominant polycystic kidney disease

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in the patients with non-ADPKD renal failure and three in the general surgical population. The overall prevalence of abdominal wall hernia in the patients with ADPKD was 45 per cent, compared with 8 per cent for those with non-ADPKD renal failure and 4 per cent for the general surgical population ($P<0{\cdot}001$). There was also a significant difference in the numbers of inguinal ($P<0{\cdot}001$), incisional ($P=0{\cdot}019$) and paraumbilical ($P=0{\cdot}007$) hernias in the patients with ADPKD compared with the other two groups.

In patients with renal failure the number of hernias before diagnosis was documented and compared with the number that occurred after diagnosis of renal disease. For patients in the ADPKD cohort, 18 of the 41 hernias were detected before the diagnosis of renal disease and 12 of these 18 presented in childhood.

All hernias that developed before the diagnosis of renal disease presented with a visible swelling; none was incarcerated or strangulated. In cases of herniation identified after the start of renal replacement therapy, all incisional and paraumbilical hernias presented as visible swellings as did inguinal hernias in patients receiving haemodialysis and transplantation of both ADPKD and non-ADPKD cohorts. In patients on CAPD, two with ADPKD and one with non-ADPKD renal failure presented with genital oedema and required radiological imaging to confirm the hernia.

Discussion

Patients with ADPKD usually present with renal impairment in the third or fourth decade and up to 50 per cent develop renal failure by the age of 60 years[2]. ADPKD is one of the commonest causes of renal failure and represents approximately 13 per cent of all cases of renal replacement therapy[3].

The characteristic features of ADPKD are large numbers of epithelial-lined renal cysts arising from the nephrons and collecting ducts. In addition to renal cysts there are a number of well recognized extrarenal associations such as hepatic and pancreatic cysts, colonic diverticula, cardiac valvular anomalies and intracranial aneurysms[1].

In 1985 genetic linkage studies[4] identified a locus for ADPKD on the short arm of chromosome 16 which is responsible for over 90 per cent of cases[5]. While the gene product is yet to be identified, it appears to regulate basement membrane and extracellular matrix production since changes in these have been described in both human and animal models of ADPKD[6–8].

Many series and case reports have documented abdominal wall hernias, mainly catheter-site herniation but also inguinal and paraumbilical hernias, in patients undergoing CAPD. Several reviews suggest an overall incidence of up to 43 per cent for adult patients on CAPD with as many as 13 per cent presenting with strangulated or incarcerated hernia[9,10].

An association between ADPKD and abdominal wall herniation is not widely recognized although such a relationship exists for other defects of collagen metabolism such as Ehlers–Danlos and Marfan's syndromes[11]. Modi *et al.*[12] in a study of patients undergoing CAPD noted an increased incidence of inguinal hernia in those with ADPKD compared with controls without such disease.

The present results show that patients with ADPKD have a statistically greater incidence of hernia both before the manifestation of renal disease and while undergoing replacement therapy compared with patients with non-ADPKD renal failure and general surgical controls. The prevalence for patients with non-ADPKD renal failure of 8 per cent compares with previous series[9,10], and the rate for inguinal hernia in the general surgical population of 4 per cent is comparable to UK figures, which suggest that by the age of 65 years 3 per cent of men will have had an inguinal hernia repair[13]. The majority of patients presented with an abdominal wall swelling although three (two with ADPKD, one without) presented with genital oedema, a presentation first recognized by Cooper *et al.*[14]. None developed a strangulated or incarcerated hernia although this has been the mode of presentation in other patients receiving CAPD at this institution[15].

A number of factors may account for the increased incidence of hernia in patients on CAPD. The processus vaginalis, which is patent in approximately 90 per cent of males at birth but which closes leaving only a 20 per cent patency rate in adults[11], may be reopened by the pressure of the dialysate[9,10,12]. Twardowski and colleagues[16] have demonstrated that the mean intra-abdominal pressure is increased during CAPD. Other possible factors include uraemia, obesity, transperitoneal protein loss and chronic anaemia. However, these factors are common to both ADPKD and non-ADPKD cohorts.

The volume occupied by the polycystic kidneys, and in some cases a polycystic liver, may contribute to an increase in intra-abdominal pressure and thus predispose to herniation. However, these results have shown that almost half of patients have developed a hernia before the diagnosis of ADPKD; many occurred in childhood prior to cyst development. A generalized weakening of the substance of the abdominal wall related to an abnormality of extracellular matrix production may be responsible for the high prevalence of herniation.

There is a significantly increased incidence of all types of abdominal wall hernia in patients with ADPKD compared with the general surgical population and other patients with impaired renal function. This is an additional extrarenal feature of ADPKD, which might have been anticipated because the disease involves an abnormality of basement membrane or extracellular matrix production. Extra vigilance for the detection and management of hernias is recommended in these patients.

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Methods of replacing blocked hepatic artery catheters

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Background Regional chemotherapy using hepatic artery catheters is one method of treating patients with colorectal liver metastases. A problem arises when the catheter occludes in patients who are responding to treatment. This report describes experience of replacing occluded hepatic artery catheters.

Methods Some 108 patients with colorectal liver metastases had hepatic arterial catheters surgically implanted for regional chemotherapy. The catheter occluded in 17 patients at a time when they were responding to treatment. Twelve catheters were replaced, of which seven were inserted retrogradely into the splenic artery, four were anastomosed end to side to the common hepatic artery via a saphenous vein graft and one was replaced in the patent gastroduodenal artery.

Results The mean duration of catheter survival when a saphenous vein graft was used was 9·6 months compared with 2·5 months following retrograde insertion into the splenic artery.

Conclusion Replacement of hepatic artery catheters is possible and may be of benefit in patients whose catheters fail while they are responding to treatment. The use of a saphenous vein graft appears to be a more anatomical and therefore preferable method of replacement than retrograde splenic artery cannulation

The results of conventional systemic chemotherapy for multiple colorectal liver metastases are disappointing[1]. Colorectal liver metastases are predominantly supplied from the hepatic artery[2] and since it is known that 5-fluorouracil has a steep dose–response curve, the use of intra-arterial therapy in these patients would seem rational. Recent studies have confirmed that intra-arterial therapy administered via a surgically implanted hepatic artery catheter is associated with prolonged survival compared with conventional palliation[3] and increased response rates compared with conventional systemic therapy[4].

Although the incidence of catheter-related complications is relatively low, a problem arises when the hepatic artery catheter thromboses in patients who are responding to intrahepatic arterial regional chemotherapy. In the authors' experience thrombolysis is unsuccessful. This report describes experience of replacing thrombosed hepatic artery catheters in such patients.

Patients and methods

Some 108 patients had implantable silicone catheters (Infusaid arterial catheter, Shiley Infusaid, Norwood, Massachusetts, USA or Jet Port Plus hepatic catheter, Meadox, Dunstable, UK) inserted for biopsy-proven colorectal liver metastases over a 5-year period. Patients underwent laparotomy through a midline or right subcostal incision and the gastroduodenal artery, right and left hepatic arteries were identified and controlled with slings. In patients with conventional anatomy (i.e. the gastroduodenal artery arising at least 2 cm proximal to the bifurcation of the right and left hepatic arteries), a catheter was inserted retrogradely into the gastroduodenal artery until its tip lay just short of the common hepatic artery. The subcutaneous injection port was placed in the right upper quadrant overlying the ribs.

Ultimately the catheter occluded in 70 patients; in 17 cases occlusion occurred at a time when the patient was showing a response to treatment and had no clinical evidence of extrahepatic disease on restaging. The mean time to catheter occlusion in these 17 patients was 7·3 (range 2–17) months. The treatment options were discussed with the patients and all patients opted for catheter replacement. Selective coeliac angiography was performed. In five patients thrombus had extended into the common hepatic artery and they were therefore considered unsuitable for catheter replacement. Catheter replacement was attempted in the remaining 12 patients. Laparotomy was performed through either a midline or extended subcostal incision. Adhesion formation was often marked, especially if there had been leakage of the catheter with chemical peritonitis.

At laparotomy an aneurysm of the common hepatic artery was encountered in one patient which precluded catheter replacement. Of the remaining 11 patients, one had a patent proximal gastroduodenal artery and the catheter was reinserted into this vessel. In four patients the hepatic artery proximal to the occluded gastroduodenal artery was identified and a saphenous vein graft was anastomosed end to side to the common hepatic artery approximately 2 cm proximal to the origin of the gastroduodenal artery[5]. The free end of the graft was cannulated with the replacement catheter which was positioned so the tip lay flush with the anastomosis. The catheter was connected to the old subcutaneous injection port. In the remaining seven patients extreme fibrosis was encountered around the hepatic artery and identification of anatomy was difficult. The catheter was therefore inserted retrogradely into the splenic artery so that the tip of the catheter lay at the origin of the splenic artery. The seven patients included one patient in whom catheters were replaced on two separate occasions, initially using a vein graft and subsequently through the splenic artery. There was no difference in the degree of hepatic replacement between the groups. The decision to use one or other technique was based on whether or not access to the common hepatic artery was feasible. In all patients adequate perfusion of the liver was ensured by the injection of patent blue dye.

Results

The survival of the catheters and patients after recatheterization is shown in *Table 1*. Mean catheter survival when saphenous vein graft was used as a conduit was 9·6 (range 1·5–23) months; following retrograde insertion into the splenic artery it was 2·5 (range 0–8) months. No

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Table 1 Method of catheter replacement, and catheter and patient survival

Patient no.	Replacement	Catheter survival (months)	Patient survival (months)
1	Vein graft	23	25
2	Vein graft	3	3
3	Splenic artery	2	3
4	Splenic artery	0	3
5	Vein graft	11	26
6	Splenic artery	8	10
7	Splenic artery	1·5	7
8	Splenic artery	4	7
9	Splenic artery	0·25	18
10	Vein graft	1·5	26
11	Gastroduodenal artery	10	10
12	Splenic artery	2	24

major complications related to the procedure were encountered and the mean patient survival after recatheterization was 14·3 (range 3–26) months.

Discussion

The main problem encountered in patients undergoing intra-arterial chemotherapy for colorectal liver metastases[6] occurs when a patient who is responding to chemotherapy and has no evidence of extrahepatic disease develops catheter thrombosis. If the common hepatic artery is patent then catheter replacement is feasible. Technically this is a difficult procedure, especially if there has been catheter leakage and the development of dense adhesions in the upper abdomen.

Although the numbers of patients undergoing each method of catheter replacement are too small to compare the two methods statistically, they represent all eligible patients in a tertiary referral centre over a 5-year period. Of the two methods used to replace hepatic artery catheters, the use of a saphenous vein graft appears to be the more satisfactory and anatomical method of replacement. What happens to the graft thereafter is unclear. Whether it is sustained by blood from the hepatic artery or cicatrizes is not known. A short length of Dacron (Du Pont, Stevenage, UK) or GORE-TEX (W.L. Gore, Woking, UK) might be equally suitable.

Retrograde insertion into the splenic artery appears to be less satisfactory. Using this technique overall catheter survival was less than 3 months, and the catheter failed immediately in one patient.

It is concluded that replacement of hepatic artery catheters is possible and may be of benefit in patients whose catheters fail whilst they are responding to treatment. However, the procedure is technically challenging and should only be undertaken in specialist centres that have expertise in dealing with this problem.

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Prospective study of hepatobiliary scintigraphy and endoscopic cholangiography for the detection of early biliary complications after orthotopic liver transplantation

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Background Biliary complications are a significant cause of morbidity and death after orthotopic liver transplantation (OLT). This study was a prospective evaluation of endoscopic retrograde cholangiography (ERC) and hepatobiliary scintigraphy (HBS), using ^{99m}Tc Mebrofenin, to detect early biliary complications following OLT.

Methods One hundred consecutive patients who had OLT with a biliary duct-to-duct anastomosis were studied. Of these, 67 had both ERC and HBS performed within 30 days of OLT. Sensitivity, specificity and diagnostic accuracy of HBS in identifying biliary leak or stricture was calculated.

Results Of the 67 cholangiographies performed 45 were normal. In 22 patients there was radiological evidence of a leak ($n = 14$) or stricture ($n = 8$) which required further intervention in nine and four patients respectively. The sensitivity and specificity of scintigraphy for the detection of biliary leak after transplantation was 50 and 79 per cent and for biliary stricture 62 and 64 per cent respectively. No patient with normal scintigraphy required biliary intervention. Only six of 14 patients with biliary leaks and two of 20 with strictures suggested by scintigraphy required intervention. If both ERC and HBS reported leak or stricture, the intervention rate was considerably higher at five of seven leaks and two of five strictures.

Conclusion This study suggests that scintigraphy is a useful screening test for biliary complications after OLT. ERC is only necessary if HBS is abnormal.

The best method of reconstructing the biliary tract after orthotopic liver transplantation (OLT) is controversial and much debated, but duct-to-duct anastomosis without a T tube is being performed with increasing frequency[1–3]. This most ‘anatomical’ reconstruction preserves the function of the sphincter of Oddi and prevents reflux cholangitis. Biliary complications are a major cause of postoperative complications and death in liver transplant recipients[3–5]. Bile leaks, in the presence of immunosuppression, may result in fatal septicaemia[4]. Early diagnosis and treatment is mandatory, but difficult in the complex circumstances of liver transplantation. Liver function tests in the period after transplantation are influenced by preservation damage, acute rejection and infection. Abdominal ultrasonography or computed tomography can detect biliary tract dilatation or a fluid collection, but major abnormalities may be missed[6,7]. The current investigation of choice to detect biliary leak or stricture is cholangiography[8–11].

Cholangiography, either endoscopic retrograde or percutaneous, is invasive and has associated morbidity. Non-invasive hepatobiliary scintigraphy (HBS) is therefore an attractive option which has proved useful for assessing biliary reconstruction but not previously in liver transplant recipients[12].

The aim of this study was to compare the value of HBS with endoscopic retrograde cholangiography (ERC) in the detection of early biliary complications after OLT.

Patients and methods

Between August 1992 and January 1995 100 patients undergoing liver transplantation at this hospital received duct-to-duct biliary anastomosis without a T tube. All donor livers were preserved in ice with lactobionate/raffinose preservation solution and transplanted according to a standard protocol. Biliary anastomosis was performed after venous and arterial revascularization of the graft using 5/0 polydioxanone suture. Standard immunosuppression consisted of prednisolone, azathioprine and cyclosporin A. Episodes of acute rejection were treated with three daily doses of methylprednisolone 1 g. All patients were scheduled to have both HBS and cholangiography 2 weeks after the liver transplantation. HBS was performed using 150 MBq ^{99m}Tc Mebrofenin (Bridateck; Sorin Biomedica, Saluggio, Italy). All images were obtained after an 8-h fast with the patient supine and using a camera with a large field of view. The arterial phase was imaged using 1-s frames This was followed by 1-min frames until 60 min after injection. At the end of the hour erect anterior and right lateral static images were obtained. Late images were performed if indicated. All images were reported without knowledge of the clinical condition by two experienced nuclear medicine consultants who provided a consensus report as normal, leak, stricture or cholestasis.

ERC was performed with Olympus (Olympus Optical, Tokyo, Japan) TJF-10 and JFIT10 scopes with antibiotic cover (intravenous mezlocillin 2 g). The results were reported by a single experienced endoscopist as normal, leak or stricture.

The form of treatment of the biliary complications was dependent on the patient's clinical condition and liver function test results as well as the result of cholangiography and scintigraphy. Patients who were clinically well, with stable graft function as indicated by standard liver function tests, and in whom radiological imaging suggested a focal anastomotic leak or stricture with no proximal bile duct dilatation, were treated conservatively. Patients with extensive leaks on initial injection of

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contrast or strictures with proximal bile duct dilatation, progressive obstructive liver function tests or who showed clinical evidence of peritonitis or sepsis were treated surgically or endoscopically. Patients who underwent laparotomy had Roux-en-Y biliary reconstruction or occasionally T tube insertion. Endoscopic treatment consisted of insertion of a nasobiliary tube or stenting for leaks and balloon dilatation for strictures.

The accuracy of HBS in detecting biliary abnormalities was assessed by comparing its findings with the results of cholangiography. The sensitivity, specificity and overall accuracy of HBS were calculated for the diagnosis of biliary stricture or leak, with the ERC findings being taken as the 'gold standard'.

Results

Over a 30-month period 100 patients were recruited for this study; their age, sex, cause of liver failure and graft cold ischaemic time are shown in *Table 1*.

Of these, 67 had both endoscopic cholangiography and HBS performed within 30 days of liver transplantation. Scintigraphy was performed between postoperative days 8 and 29 (median day 12) and cholangiography between days 12 and 30 (median day 17). Thirty-three of the 100 patients were excluded from further analysis. These patients did not have both ERC and HBS within the 30-day period. In 18 of these patients there was no biliary tract imaging and in 15 either ERC or HBS alone was performed. There were many factors responsible for ERC and HBS not being performed in this group of patients. These included postoperative death, the patient being too unwell to attend for the tests, non-availability of either ERC or HBS, inability to tolerate endoscopy and technical difficulty in cannulating the ampulla. In some patients several factors were responsible. There were no early biliary tract complications that required intervention in this group of patients.

Table 1 Patient characteristics

Age (years)*	47 (6–68)
Sex ratio (M·F)	66:34
Cause of liver failure	
Primary biliary cirrhosis	12
Hepatitis C	31
Primary sclerosing cholangitis	16
Alcoholic cirrhosis	17
Other†	24
Graft cold ischaemic time (min)*	759 (210–1227)

*Values are median (range). †Caroli, cryptogenic, hepatitis B virus, fulminant, Budd–Chiari syndrome, chronic autoimmune hepatitis, chronic rejection, amyloidosis

Table 2 Comparison of hepatobiliary scintigraphy and endoscopic cholangiography findings after orthotopic liver transplantation

	Endoscopic retrograde cholangiography		
	Normal	Leak	Stricture
Hepatobiliary scintigraphy			
Normal	27	3	0
Leak	5	7	2
Stricture	11	4	5
Cholestasis	2		1

Table 3 Accuracy of hepatobiliary scintigraphy in diagnosing early biliary complications compared with cholangiography

	Leak	Stricture
Sensitivity (%)	50	62
Specificity (%)	79	64
Overall accuracy (%)	71	63

There were no complications related to HBS. One patient developed mild acute pancreatitis following ERC which settled with conservative treatment. The results of scintigraphy and cholangiography are shown in *Table 2*. The sensitivity, specificity and overall diagnostic accuracy of HBS are shown in *Table 3*.

Of the 67 cholangiographies performed 45 showed a normal postoperative biliary tract. In 22 there was radiological evidence of a leak ($n = 14$) or stricture ($n = 8$). In the 45 patients with normal cholangiography, scintigraphy correctly reported a normal biliary tract on 27 occasions. On five occasions scintigraphy suggested a leak, on 11 occasions a stricture and twice cholestasis. On three occasions HBS was normal but ERC demonstrated a leak. HBS detected seven of 14 biliary leaks seen on cholangiography. In seven patients scintigraphy reported a leak but ERC was normal ($n = 5$) or revealed a stricture ($n = 2$). Sensitivity and specificity of scintigraphy in detecting biliary leaks, compared with ERC, were 50 and 79 per cent respectively. Overall accuracy was 71 per cent.

HBS reported strictures in five of eight patients confirmed by cholangiography (sensitivity 62 per cent), and only two of these five required intervention. In 11 patients scintigraphy reported a stricture whereas ERC showed no abnormality. In four patients scintigraphy showed a stricture but ERC revealed a leak (specificity 64 per cent). Overall accuracy of HBS for detecting biliary stricture was 63 per cent

If scintigraphy had been the sole test employed for the detection of biliary complications in patients following liver transplantation only 39 of 67 patients (58 per cent) would have been correctly diagnosed. On the 30 occasions when HBS was reported as normal, no patient required early biliary intervention. Similarly, none of the 45 patients with a normal ERC required treatment for early biliary complications.

Scintigraphy reported 14 bile leaks, but only six required intervention (five leaks and one stricture shown on cholangiography). On the eight occasions when a scintigraphic leak did not result in intervention, cholangiography showed a leak in two, stricture in one and five were normal. Of the 14 biliary leaks diagnosed on cholangiography, nine required further treatment. Intervention was required in five of seven leaks shown by both investigations.

Of the 20 patients with strictures suggested by scintigraphy, only five were confirmed by cholangiography, and only two required intervention. The remaining 15 patients had either normal ERC ($n = 11$) or an anastomotic leak ($n = 4$). The intervention rate for strictures diagnosed on scintigraphy was 10 per cent and 50 per cent for those diagnosed by cholangiography. Two of five strictures shown by both investigations required intervention.

A cholestatic picture on scintigraphy interfered with the assessment of biliary complications in three patients, one of whom had a stricture which required treatment.

Discussion

There is no evidence to support the use of T tubes following OLT[1–3] but direct duct-to-duct biliary anastomosis without a T tube requires endoscopic or percutaneous cholangiography to be performed for the diagnosis of biliary leak or stricture[8,10,11]. Although some patient groups have been suggested as having a higher incidence of biliary tract complications, such as those with primary sclerosing cholangitis[13], the authors' experience suggests that primary duct-to-duct anastomosis is not associated with an increased risk of biliary complications in this group[14] and there is no satisfactory method of predicting those patients likely to have biliary tract problems. Biliary complications following liver transplantation are life threatening and require immediate diagnosis and treatment[3–5]. Endoscopic and percutaneous cholangiography have an associated morbidity and mortality rate and non-invasive methods of detecting biliary complications are therefore required[15,16]. HBS is a non-invasive investigation which has been used previously to diagnose complications after biliary tract surgery[12]. It has not previously been evaluated for the detection of complications after liver transplantation in a prospective controlled study.

Both HBS and endoscopic cholangiography were performed successfully in the majority of patients within 30 days of liver transplantation with minimal morbidity and no deaths. The exclusion of one-third of the patients from the study was mainly because either the patients were not fit enough to withstand the investigations, or nuclear medicine or radiology facilities were not available during the study period.

This study has shown that a scintigraphic diagnosis of normal biliary anatomy after OLT could be confirmed by cholangiography in the majority of patients. Of critical importance to clinical practice is that no patient with a normal scintigram required surgical or radiological intervention. The three patients with biliary leaks on cholangiography and a normal scintigram were clinically well and did not require treatment. A normal scintigram could therefore be missing small leaks, but these do not seem to be clinically significant, suggesting that scintigraphy is a satisfactory method of screening for early biliary tract complications following OLT. Cholangiography in the early period after OLT appears to be a good predictor of biliary tract complications; none of the 45 patients with normal cholangiography required surgery for biliary tract problems in the first 2 months after transplantation. How late biliary tract complications will relate to early ERC findings remains to be established.

In this series, scintigraphy detected only half of the biliary leaks seen on cholangiography and also suggested their presence where none was seen on cholangiography. A possible explanation for false-negative HBS results is that cholangiographic contrast injected under pressure visualizes small leaks which may not be clinically relevant, whereas positive scintigraphy requires significant accumulation of radioisotope outwith the biliary tree which would occur only with larger biliary leaks. False-positive results, on the other hand, may be produced by radioisotope refluxing into the duodenum, which can be interpreted as a leak into the subhepatic area. The low sensitivity and specificity of HBS would suggest that cholangiography should be performed in all patients in whom HBS is abnormal. Leaks confirmed on both tests are likely to be significant and will require intervention in approximately two-thirds of patients.

The scintigraphic suggestion of a biliary stricture correlated poorly with the findings at cholangiography and the need for subsequent intervention. This suggests that a diagnosis of biliary stricture on the basis of HBS findings is not appropriate. The intervention rate for strictures reported on either of the imaging modalities was low, and did not improve when the results of tests were combined. This suggests that strictures diagnosed in the early period after transplantation by scintigraphy or cholangiography are often of no clinical significance However, strictures associated with cholangitis, obstructive liver function tests or a dilated intrahepatic biliary tree were considered an indication for intervention in this study.

Intrahepatic cholestasis has previously been suggested as a problem with the use of scintigraphy as a diagnostic test after liver transplantation. However, the newer generation of radioisotope imaging agents (e.g. Mebrofenin) could provide imaging in the majority of patients in this study[17].

It is concluded that HBS is a simple, safe, practical and non-invasive screening investigation for biliary complications after liver transplantation. A normal result suggests a satisfactory reconstruction of the biliary tree after OLT and avoids the need for cholangiography. Abnormal scintigraphy is an indication for cholangiography.

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Outcome of surgery for chronic pancreatitis

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Background In patients with chronic pancreatitis, surgery is indicated for the management of intractable pain or for the treatment of complications.

Methods Sixty-three consecutive patients (49 men and 14 women of median age 40 (range 20–72) years) who had undergone surgery over an 8-year interval for chronic pancreatitis were studied. The mortality and morbidity rates associated with surgery were assessed and quality of life was reviewed based on relief of symptoms, analgesic use, employment and long-term sequelae.

Results Forty-four patients (70 per cent) had alcoholic chronic pancreatitis. In 60 patients the principal indication for surgery was intractable pain. Eighteen patients had a duodenum-preserving resection of the pancreatic head (Beger operation); the other surgical procedures were Whipple resection (15), left-sided resection (13), total pancreatectomy (seven), pseudocystjejunostomy (five), pancreaticojejunostomy (one) and bypass procedures (four). The median inpatient stay was 12 days; 23 patients had postoperative complications including one death (2 per cent). There was improved pain control ($P < 0\cdot001$), a reduction in opiate analgesia use, increase in percentage weight gain ($P < 0\cdot01$ at 2 years) and return to employment following surgery. Although there was an increase in diabetes mellitus and need for enzyme supplementation these were easily controlled.

Conclusion Surgery is an effective treatment in carefully selected patients with chronic pancreatitis but must be tailored to the pattern of disease in each individual.

The management of patients with chronic pancreatitis remains a difficult and challenging problem. In most cases the disease is the result of chronic alcohol abuse and patients are often addicted to opiates by the time of surgery because of chronic pain. The principal indication for surgery in chronic pancreatitis is intractable pain which prevents the patient from leading a normal life[1]. Less frequently, surgery is indicated for the treatment of the complications of chronic pancreatitis including pseudocyst, pancreatic fistula, splenic vein thrombosis and duodenal or biliary obstruction[2].

Before 1980, pancreatic surgery was associated with an operative mortality rate of up to 25 per cent and the results of surgery were unpredictable, with many patients continuing to suffer from severe pain often associated with marked endocrine and exocrine insufficiency[3–5]. Although conservative treatment may be successful in some patients with chronic pancreatitis if spontaneous remission of pain occurs[6], its timing is unpredictable and the patient may lose valuable years of life.

The use of endoscopic retrograde cholangiopancreatography (ERCP) and computed tomography (CT) has enabled the pattern of disease to be determined with increased accuracy before surgery[7–9]. Operations can be tailored to the particular pattern of disease in an individual patient and may be associated with a better long-term outcome[10] with a minimal mortality rate in specialist units[11]. Several centres report an operative mortality rate below 5 per cent for pancreaticoduodenectomy[12–19] including a number of institutions with no perioperative deaths in large series of patients[10,20–23]. Postoperative morbidity, however, remains high after these procedures although most complications are amenable to treatment. More recently new procedures have been developed for the management of chronic pancreatitis including pylorus- or duodenum-preserving resection of the head of the pancreas and spleen-preserving left pancreatic resection, designed to reduce the pathophysiological effects of resection[24–26].

This is a largely prospective study that analyses the medium-term outcome of surgery for chronic pancreatitis with particular emphasis on the quality of life for patients based on the mortality and morbidity rates associated with surgery, relief of symptoms, analgesic use, employment and long-term sequelae of pancreatic surgery.

Patients and methods

Sixty-three consecutive patients who had surgery for chronic pancreatitis between 1988 and 1995 in Birmingham were studied. Forty-five patients under the care of one author (J.P.N.) were studied prospectively. They were assessed initially before surgery and then in the outpatient clinic at 6 weeks, 3 months, 6 months, 1 year and annually thereafter. Data were recorded on a preprinted standard sheet with particular reference to: aetiology; operative morbidity and 30-day mortality rates; reoperation rate; severity of abdominal pain (graded from 0 (none) to 4 (unbearable)); frequency and type of analgesia used; weight gain; employment; endocrine or exocrine insufficiency and use of supplements; alcohol consumption; hospital admissions; social problems; co-existent medical disease; and the number and cause of late deaths. A further 18 patients under the care of three of the authors (P.M., A.D.M., J.A.C.B.) were assessed retrospectively using the same parameters. Diabetes mellitus was defined using World Health Organization criteria. Exocrine insufficiency was assessed clinically by the presence of gross steatorrhoea supplemented by pancreatic function tests. Alcoholic chronic pancreatitis was defined as chronic pancreatitis associated with the consumption of greater than 50 units of alcohol per week for at least 5 years with no other aetiological

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factor. The diagnosis of chronic pancreatitis was established by preoperative ultrasonography, CT and ERCP. This was supplemented by inspection of the gland at the time of surgery and intraoperative ultrasonography where indicated The diagnosis was confirmed by histological examination after biopsy or resection in all cases

Data were analysed using one-way analysis of variance, χ^2 test, Fisher's exact test, Student's t test and the one-sample t test

Results

There were 49 men and 14 women with a median age of 40 (range 20–72) years. Forty-four patients (70 per cent) had alcohol-induced chronic pancreatitis, 15 (24 per cent) idiopathic disease and four patients (6 per cent) had rare causes (primary hyperparathyroidism, primary biliary cirrhosis, choledochal cyst and familial chronic pancreatitis). The median duration of symptoms before surgery was 24 (range 1–240) months. In 60 patients (95 per cent) the principal indication for surgery was chronic intractable pain. Common associated symptoms included jaundice in 13 patients (21 per cent) and gross exocrine insufficiency in 24 (38 per cent). Fourteen patients (23 per cent) had endocrine insufficiency before surgery including nine (15 per cent) who were dependent on insulin. Fifty-six patients (90 per cent) were taking regular daily oral analgesia at the time of surgery including 28 (45 per cent) on strong oral opiates and 28 (45 per cent) on daily moderate analgesics (co-proxamol, dihydrocodeine, buprenorphine); one patient (2 per cent) was on occasional (less than daily) oral analgesia and five (8 per cent) were on no regular analgesia. Forty-four (77 per cent) of 57 patients of working age were unemployed at the time of surgery. Preoperative investigations demonstrated the presence of a pseudocyst in 17 patients (30 per cent) and pancreatic calcification in 23 (42 per cent). Ten patients had significant co-existent medical disease including hypertension (five), peptic ulcer disease (two), cirrhosis and portal hypertension (one), angina (one), asthma (one) and chronic renal failure (one)

Fifty-three patients (84 per cent) had a resection of the diseased part of the gland, most often right sided, which included 15 (24 per cent) Whipple resections of which three were pylorus-preserving and 18 (29 per cent) Beger operations (duodenum-preserving resection of the head of the pancreas). There were 13 (21 per cent) left-sided resections in which 40–80 per cent of the gland was excised (four were spleen preserving) and seven (11 per cent) total pancreatectomies (one conventional, two spleen-preserving, two duodenum-preserving and two duodenum- and spleen-preserving resections). The remaining ten patients (16 per cent) had drainage procedures; there were equal numbers of pseudocystjejunostomies and bypass procedures.

There were a total of 29 complications in 23 patients (morbidity 37 per cent) within the perioperative period (*Table 1*). The presence of a pancreatic fistula was defined by the production of greater than 50 ml abdominal fluid per day with an amylase content of greater than 1000 units per litre (normally less than 300 units per litre). Six patients required further surgery, two in the early postoperative period. One required a relaparotomy for bleeding and recovered satisfactorily; the other had a laparotomy for biliary peritonitis and subsequently died giving a hospital mortality rate of 2 per cent. Of the other four patients, two required conversion to total pancreatectomy for intractable pain at 2 months and 2 years after a Beger and Whipple operation respectively, one developed a stenosis of the enteroenterostomy 3 years after a Whipple procedure and required refashioning of the anastomosis, and the final patient had excision of a stitch sinus 2 years after operation. There were four late deaths during the follow-up period. One patient addicted to heroin before operation, who continued to abuse alcohol following surgery but without abdominal pain, died 2 years after the operation from a heroin overdose. Three other patients died, one each from cerebrovascular accident, gastric carcinoma and small bowel lymphoma.

After operation there was a reduction in the number of patients who had regular pain after all surgical procedures ($P < 0{\cdot}001$) (*Fig. 1*) but there was no statistically significant difference between the procedures. In patients who continued to experience pain after surgery this was generally less severe and there was a reduction in the

Table 1 Postoperative complications

Complication	Whipple ($n = 15$)	Beger ($n = 18$)	Left resection ($n = 13$)	Bypass/drainage ($n = 10$)	Total pancreatectomy ($n = 7$)	Total no of complications
Pulmonary						
Atelectasis		1	1			2 (3)
Pneumonia	3	1				4 (6)
Pneumothorax	1	1				2 (3)
Gastrointestinal						
Biliary leak	2	2			1	5 (8)
Pancreatic fistula	1			1		2 (3)
Haemorrhage	1	2	1		1	5 (8)
Gastrointestinal haemorrhage		1	1			2 (3)
Subphrenic abscess	1					1 (2)
Gastric stasis		1				1 (2)
Others						
Septicaemia	1			1		2 (3)
Pressure sore				1		1 (2)
Wound infection	1	1				2 (3)
Total	11	10	3	3	2	29

Values in parentheses are percentages of all patients median pain score from 4 (unbearable) before operation to 0 (none) after operation which was maintained on follow-up ($P<0{\cdot}0001$). There was a significant reduction in the use of all types of analgesia following surgery (*Fig. 1*) with only two patients (5 per cent) at 1 year remaining on opiates ($P<0{\cdot}01$). The number of patients on no regular analgesia increased from five (8 per cent) of 62 before operation to 19 of 30 at 2 years after surgery ($P<0{\cdot}001$).

There was a significant reduction in alcohol consumption after surgery with only one-third of patients continuing to drink alcohol beyond 1 year after surgery ($P<0{\cdot}0001$) (*Fig. 2*). There was no significant difference in pain score between those who continued to drink and those who abstained. There was an increase in the percentage weight change after surgery compared with the preoperative weight (*Fig. 3*) but there was no significant difference between the different types of surgical resection or between resection and drainage procedures.

There was a significant increase in those in regular employment after surgery ($P<0{\cdot}02$). Although this appeared to fall off at 4 years, the number of patients still under follow-up at this time was small (*Fig. 4*).

The median number of hospital admissions fell after surgery for all procedures from two admissions per year to none ($P<0{\cdot}0001$) by 12 months after surgery, which was maintained during follow-up.

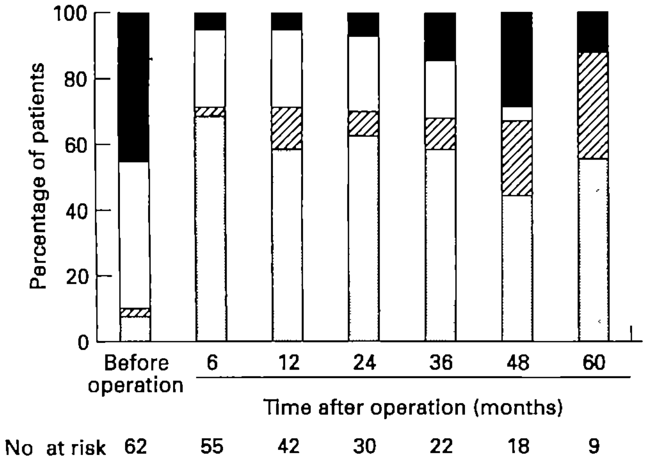


Fig. 1 Analgesia required before and after surgery for chronic pancreatitis. □, None; ▨, occasional moderate analgesia; □, daily moderate analgesia; ■, daily strong analgesia. $P<0{\cdot}01$ (number of patients taking opiates *versus* no opiates over a 5-year period), $P<0{\cdot}001$ (number of patients taking no regular analgesia *versus* analgesia over a 5-year period) χ^2 for trend

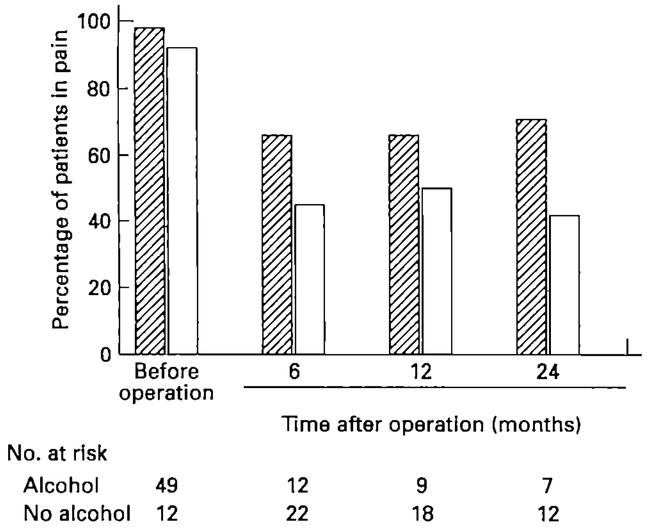


Fig. 2 Effect of alcohol consumption on pain after surgery. ▨, Alcohol drinkers, □, abstainers. There was no significant difference in pain score between patients who drank alcohol and those who abstained. χ^2 for trend

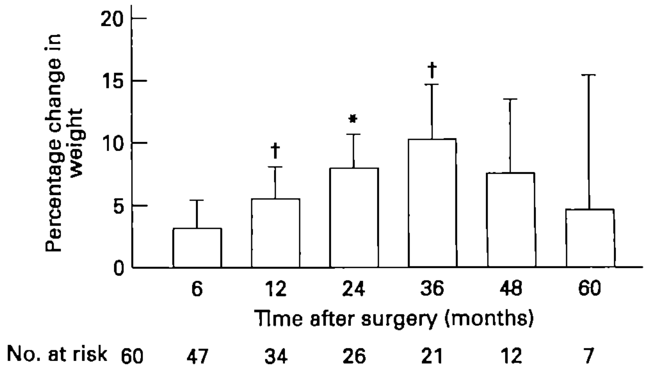


Fig. 3 Percentage change in weight after surgery. $^*P<0{\cdot}01$, $^\dagger P<0{\cdot}03$ *versus* before operation. One sample *t* test

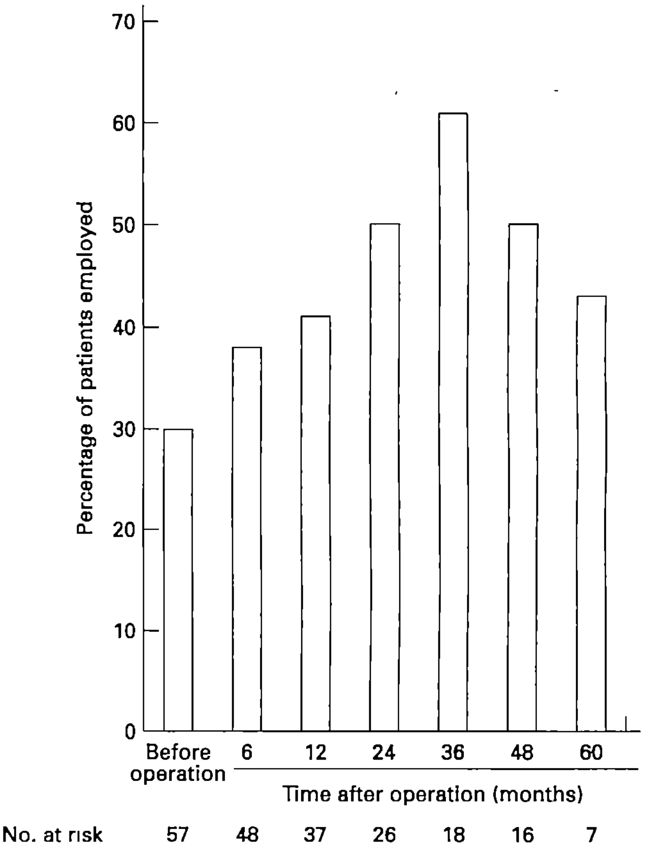
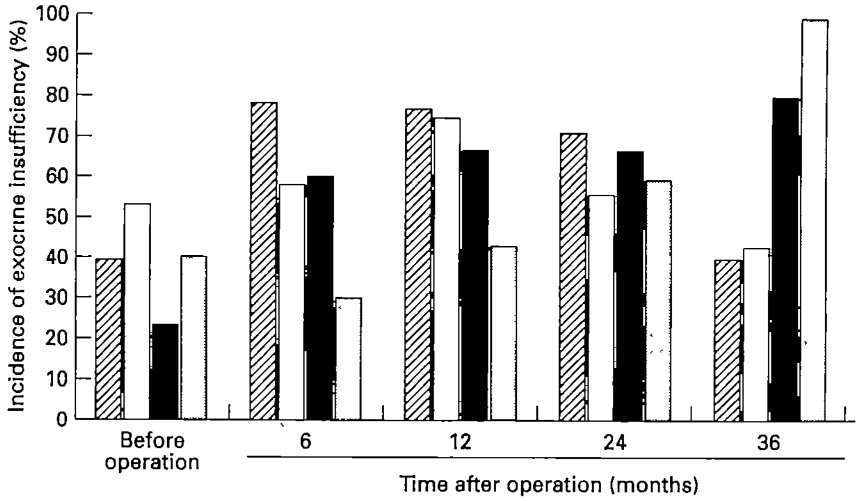


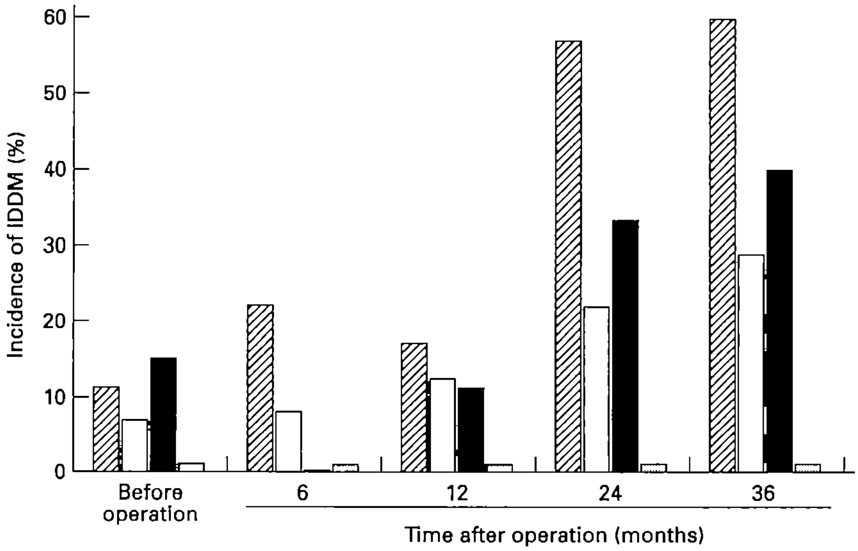
Fig. 4 Employment before and after surgery for chronic pancreatitis. $P<0{\cdot}02$ (before *versus* after surgery). χ^2 for trend

Following surgery, there was a significant increase in the number of patients prescribed exocrine supplements for all procedures but there was no difference in outcome when different operative procedures were compared (*Fig. 5*). The incidence of insulin-dependent diabetes mellitus (IDDM) increased to 11 of 30 patients by 2 years after surgery. No patient treated with a bypass or drainage operation developed IDDM but there was no significant difference between procedures (*Fig. 6*). Despite the incidence of IDDM, glycaemic control was satisfactory with no hospital admissions or deaths attributable to diabetes mellitus.



No. at risk	Before operation	6	12	24	36
Beger	18	18	13	7	5
Whipple	15	12	8	9	7
Left resection	13	10	9	6	5
Bypass/drainage	10	10	7	5	3

Fig. 5 Exocrine insufficiency before and after surgery for chronic pancreatitis. ▨, Beger operation; ☐, Whipple resection; ■, left-sided resection; ☐, bypass or drainage. $P<0{\cdot}002$ (number of patients with exocrine insufficiency *versus* no exocrine insufficiency) χ^2 for trend



No. at risk	Before operation	6	12	24	36
Beger	18	18	12	5	6
Whipple	15	12	8	9	7
Left resection	13	10	9	6	5
Bypass/drainage	10	10	7	5	3

Fig. 6 Incidence of insulin-dependent diabetes mellitus before and after surgery for chronic pancreatitis ▨, Beger operation, ☐, Whipple resection; ■, left-sided resection; ☐, bypass or drainage. $P<0{\cdot}001$ (number of patients with IDDM *versus* those with no DM or NIDDM considering all types of procedure together at each time point). χ^2 for trend

Discussion

The postoperative mortality rate in this series (2 per cent) compares favourably with results from other specialist units[10,12–23,27]. Many authors have reported a high incidence of late deaths (20–50 per cent) after surgery for chronic pancreatitis especially in patients who continue to abuse alcohol[28–30]. The most commonly reported causes of late death include cirrhosis of the liver, suicide, accidents, myocardial infarction, lung cancer and diabetic hyperglycaemic or hypoglycaemic coma[29,31–34]. One of the four late deaths in this series was related to continued alcohol abuse with heroin addiction but none was directly attributable to poor diabetic control. No patient in this series has subsequently developed pancreatic cancer during follow-up; however, since 1988 three patients who presented with presumed chronic pancreatitis were found at operation to have pancreatic cancer which was confirmed by histology following resection.

Patients with chronic pancreatitis are at risk of postoperative complications because of the nutritional and metabolic disturbances that may result from severe pancreatic insufficiency and the high incidence of smoking. The frequency of postoperative complications (37 per cent) in this series is similar to that reported in other studies[28,35,36] with most amenable to treatment and very few requiring surgical intervention.

Medically intractable pain is the most common indication for surgery in patients with chronic pancreatitis and is therefore an important parameter upon which the success of surgery should be measured. In this series left resection was performed for predominantly left-sided disease, the Whipple or Beger operation for dominant right-sided disease depending on the preference of the surgeon, total pancreatectomy for disease involving the whole pancreas associated with marked pancreatic insufficiency including the need for insulin, and pancreaticojejunostomy for patients with dilatation of the main pancreatic duct. In the past, several authors have reported a high incidence of persistent pain after left resection which resulted in criticism of the procedure. This may represent poor patient selection as each patient has a different pattern of disease which requires an individually designed operation. More recent series demonstrate similar success in terms of pain relief for all procedures[34,37] and new operations developed to preserve the normal anatomy and physiology have achieved good results. The introduction of the pylorus-preserving pancreaticoduodenectomy by Traverso and Longmire in 1978[25] resulted in less nutritional disability and preservation of normal gastric emptying, findings that have been supported by other authors[38]. Beger *et al.*[24] introduced the duodenum-preserving resection of the head of the pancreas which spares the patient a partial gastrectomy, duodenectomy and common bile duct resection, and Frey and Amikura[39] have also reported good results using a similar procedure. Other promising organ-sparing procedures are the duodenum-preserving total pancreatectomy and spleen-preserving left resections[23,26].

In this series, most patients had a marked reduction in pain immediately after surgery which was maintained. Several other authors with the same follow-up period as this series, have reported a similar outcome for the relief of pain following surgery[1,27,32–35]. This was associated with a significant reduction in the use of all types of analgesia including opiates, and by 2 years after surgery almost two-thirds of patients were taking no regular analgesia. Several series have shown that patients with alcohol-induced chronic pancreatitis who continue to drink alcohol after surgery have a worse overall outcome[40]. In the present study those who continued to drink had higher pain scores than those who did not but the difference was not significant. This may, however, be related to the relatively small number of patients in the study who continued to drink alcohol, and the authors agree that patients must be advised to refrain from drinking alcohol.

Left resection has been associated with a high incidence of IDDM after surgery perhaps because of the said relative preponderance of islets of Langerhans within the body and tail of the pancreas[41]. Standard pancreaticoduodenectomy is associated with loss of the normal enteroinsular axis and typically results in a 20 per cent increase in the incidence of IDDM[27]. In contrast, Beger and colleagues[11] reported no significant deterioration in glucose metabolism after duodenum-preserving resection of the head of the pancreas. Higher levels of exocrine insufficiency have also been reported after left resection compared with the Whipple operation and minimal exocrine disturbance occurred after duodenum-preserving resection of the head of the pancreas[1,24,35]. The preservation of endocrine and exocrine function corresponds to the improvement in nutritional status after surgery, with Beger *et al.*[11] reporting an increase in weight in 80 per cent of patients after duodenum-preserving resection of the head of the pancreas. In this series, however, all procedures were associated with an increase in IDDM and an increase in exocrine insufficiency. Despite the increases in pancreatic insufficiency there was an increase in the percentage weight gain after all procedures.

This series demonstrates that surgery has a clear role in the management of patients with medically intractable pain or complications resulting from chronic pancreatitis. Surgery results in an increased quality of life for most patients with a reduction in pain and analgesic use, fewer hospital admissions, weight gain and an increase in regular employment. Although there is an increase in IDDM and exocrine insufficiency these are well controlled with medical treatment. Many authors have questioned the place of surgery in the management of non-malignant pancreatic disease but improvement in operative mortality and morbidity rates means that pancreatic resection is justified for the treatment of benign pancreatic disease. This difficult group of patients is best treated within a specialist pancreaticobiliary unit by a multidisciplinary approach with involvement of psychiatrists, diabetologists and dieticians in addition to the addiction organizations.

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Laparoscopic cholecystectomy and the umbilicus

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Background Pre-existing umbilical defects may present technical problems in patients having laparoscopic surgery. Fascial defects may also occur after operation. Understanding the causes and mechanisms of herniation at laparoscopic port sites may help avoid potentially serious postoperative complications.

Methods The incidence, management and potential complications of pre-existing and postoperative umbilical defects were studied in 870 patients undergoing laparoscopic cholecystectomy.

Results The incidence of umbilical or paraumbilical defects was 12 per cent. The hernias were symptomatic in only 16·3 per cent; the majority of patients were unaware of the defect. The umbilical port was established through, or directly adjacent to, the defect, allowing simple anatomical repair in 90 per cent, using absorbable sutures. The recurrence rate was 3·8 per cent; recurrence was usually caused by wound extension or infection. Incisional hernia occurred in 16 patients after cholecystectomy (1·8 per cent). Only one hernia developed at a port site other than the umbilicus. Risk factors associated with incisional hernia were wound extension in 12 patients, male sex in six, wound infection in five, diabetes in four, pre-existing umbilical hernia in four and acute cholecystitis in three.

Conclusion The significant incidence of umbilical defects in patients undergoing laparoscopic surgery calls for accurate diagnosis and good technique. The incidence of incisional hernia might be reduced by avoiding unnecessary wound extension and the use of non-absorbable sutures for defects larger than 2 cm and in men with umbilical hernia.

Umbilical fascial defects may be encountered in patients undergoing laparoscopic cholecystectomy. Such defects may be associated with umbilical hernia, present at the time of laparoscopic cholecystectomy, or with incisional hernia, developing after laparoscopic cholecystectomy. The aim of this prospective study was to identify the potential problems and optimal methods for dealing with umbilical hernia at the time of laparoscopic cholecystectomy, and to document the causes of incisional hernia and how to avoid the occurrence of this potentially serious complication after laparoscopic cholecystectomy.

Materials and methods

In a study of 870 patients undergoing laparoscopic cholecystectomy over a period of 4 years from September 1991 to August 1995, the presence of a symptomatic umbilical hernia, an asymptomatic umbilical or paraumbilical defect on examination, a history of airways disease or diabetes, or a history of previous surgery involving the umbilicus were recorded. The methods used to establish the umbilical cannula and to repair the umbilical hernia defect after laparoscopic cholecystectomy, and follow-up data, were documented. Findings were recorded on a database (d.Base III plus, version 1.1; Ashton Tate, Culver City, California, USA). Data analysis was carried out 4 months after the end of the study. The first follow-up visit was after between 2 weeks and 3 months. Special attention was paid to history or evidence of wound infection, and to examination of the umbilicus Second appointments, 2–6 months later, were given to most patients. The completeness of follow-up is potentiated by the fact that this hospital provides care to Saudi National Guards and their dependants. Patients having any problems after laparoscopic cholecystectomy could return to open access emergency or outpatient departments.

Results

The umbilicus before laparoscopic cholecystectomy

Umbilical or paraumbilical defects were found in 104 patients (12 per cent). There were 91 (87·5 per cent) women, with a mean age of 42 (range 20–68) years. There was a history of asthma or chronic obstructive airway disease in five patients, diabetes in 13 and previous repair of umbilical hernia in two. Seven patients presented with acute cholecystitis.

The presence of an obvious umbilical hernia was reported by only 17 patients. Most defects were 1·5–2 cm in size, detected on examination as fatty hernias or cough impulses. On a number of occasions, smaller defects were diagnosed on induction of pneumoperitoneum.

All operations were performed by one of four consultants, either personally or assisting five trainees. The umbilical cannula was mostly established by inserting a Veress needle and then the cannula at the lower edge of the defect. In 16 patients, an incision was made over the hernia and blunt entry into a thin sac allowed insertion of a cannula without a trocar. Larger hernia sacs had to be dissected and excised before placing the cannula through a partially closed defect. Laparoscopic cholecystectomy was performed and the hernia was repaired at the end of the procedure in seven patients.

In spite of the presence of an umbilical hernia, extension of the umbilical fascial incision to deliver an acutely inflamed gallbladder or one with a large stone was necessary in 12 patients. The fascial defect was repaired using absorbable polyglycolic acid sutures in most cases,

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while a non-absorbable monofilament suture was used in 11 patients (10·6 per cent). The mean operative time for laparoscopic cholecystectomy associated with umbilical hernia repair was 86 min, compared with 90 min for the whole series (first incision to last stitch). The incidence of postoperative wound infection was 3·8 per cent. Recurrence occurred in four cases. Wound extension had been carried out in three, while only two patients had developed wound infections.

The umbilicus after laparoscopic cholecystectomy

A total of 16 incisional hernias occurred in 870 laparoscopic cholecystectomies (1·8 per cent). Although the majority of patients were women, incisional hernias occurred in six men (37·5 compared with 19 per cent male incidence in the whole series). The mean (range) age was 48 (26–63) years. The mean (range) weight was 64·5 (38–87) kg; only one patient was considered obese, in whom incisional hernia was related to wound infection after umbilical hernia repair. Only two women were of child-bearing age but none became pregnant after laparoscopic cholecystectomy. The diagnosis of incisional hernia was made 2–18 (mean 6) months after laparoscopic cholecystectomy. None was detected at the first follow-up visit. One incisional hernia occurred at the site of the lower lateral 5-mm port, and one patient presented with acute intestinal obstruction due to an incarcerated incisional hernia at the umbilicus. The factors most frequently associated with the development of incisional hernia are shown in *Table 1*. Nine incisional hernias have so far had conventional repairs; the rest are being observed on account of their small size or because of the unwillingness of some patients to undergo further surgery.

Table 1 Risk factors associated with 16 incisional hernias following laparoscopic cholecystectomy

	No. of patients
Wound extension	12 (75)
Male sex	6 (38)
Wound infection	5 (31)
Umbilical hernia	4 (25)
Diabetes mellitus	4 (25)
Acute cholecystitis	3 (19)

Values in parentheses are percentages

Discussion

The presence of pre-existing fascial defects at the umbilicus poses a degree of technical difficulty and some potential for operative and postoperative complications, and may have important medicolegal implications. There is also increasing recognition of postoperative port-site complications, such as incisional hernia and intestinal obstruction.

Umbilical or paraumbilical defects need to be identified and dealt with, as the recognition of an untreated defect in the vicinity of the port site after operation can only be interpreted as an incisional hernia. This would cause a false increase in the reported incidence of incisional hernia after laparoscopic surgery. The medicolegal aspect is also important, as the majority of the patients in this study were not aware of the presence of an umbilical hernia. Although some authors have recognized the significance of incidental pre-existing umbilical hernia[1], there are no reports on the incidence of umbilical hernia in patients undergoing laparoscopic cholecystectomy. In this series, the 12 per cent incidence is probably high but may be explained by the prospective search for small defects, and by the majority of patients being multiparous women.

Various methods are being used for access and repair of umbilical hernia encountered during laparoscopic cholecystectomy. Repair of the hernia in a conventional manner at the end of the procedure[2] or repair through the umbilical trocar incisions[3] have been reported. The present authors used an access approach based on the size of the defect (*Table 2*). Using this approach, the majority of defects can be repaired in a manner similar to simple closure of the port fascial incision, using absorbable sutures[4].

The occurrence of incisional hernia following laparoscopic surgery is well documented. The incidence varies between 0·8 and 2·8 per cent[1,4–8] (mean 1·2 per cent), and may be as high as 3 per cent after gynaecological procedures[9–11]. Most incisional hernias (86 per cent) occurred at sites of ports 10 mm or greater. The majority of incisional hernias after laparoscopic cholecystectomy occur at the umbilicus but some have been reported at the epigastrium[8,12] or lower lateral port[4,13]. Almost all incisional hernias reported in the literature[14–18] resulted from failure to close the fascial defects. It is hoped that such a complication is now a rare occurrence as, with the exception of carefully established and undilated epigastric

Table 2 Establishing and closing the umbilical port in patients with umbilical or paraumbilical defects

Defect size	Access	Closure
Up to 15 mm Preoperative diagnosis	Skin incision over lower edge Blunt dissection to define edge Veress needle at lower edge Cannula through defect	Continuous absorbable suture
Diagnosed at surgery	Adjacent port site	Connect and repair as one defect
	Distant port site	Obliterate separately
15–25 mm	Skin incision over bulge Blunt dissection to enter sac and peritoneum under vision Insert cannula without trocar	Continuous absorbable sutures Interrupted non-absorbable for thin fascia and in men
>25 mm	Dissect and excise sac Place cannula through purse-string or repair with interrupted sutures and place cannula before last stitch	Interrupted non-absorbable sutures

port sites, no justification could now be advanced for not closing fascial defects of 10 mm or greater. Intestinal obstruction can also be caused by including the bowel wall, or the omentum, in the fascial closure stitch[19]. Incisional hernia after laparoscopic surgery can also result from the reintroduction of a displaced cannula, widening the defect or creating another which later coalesces with the original one[20]. This seems to have been the cause of a right lower port hernia in this series. De Giuli *et al*[21] suggested forced dilatation of the umbilical port, to remove the gallbladder, as an aetiological mechanism. This was the most significant risk factor in the present series. Three of the four recurrences of umbilical hernia occurred in cases where wound extension was done. The practice of incising the fascia, stretched over the umbilical cannula, which is advocated as a safe and simple method for removal of the gallbladder[22] may therefore predispose to incisional hernia.

Surgeons using the epigastrium to deliver the gallbladder argue that incisional hernia is less likely because of the presence of the liver and tissue layers[17]. However, Plaus[8] reported the highest incidence of incisional hernia (3·6 per cent), three of four such hernias occurring at the epigastric port. Furthermore, stretching or extending the epigastric incision may pose other problems such as bleeding, which can be troublesome. If the gallbladder is removed from the epigastrium rather than the umbilical incision, it is then essential to close both defects.

There seems to be no correlation between technical difficulty in performing laparoscopic cholecystectomy and development of incisional hernia, except where this difficulty is related to the presence of acute cholecystitis or empyema, necessitating wound extension or predisposing to wound infection. In this series there were only two procedures of difficulty grade III (acute cholecystitis) and one of grade IV (empyema)[23,24].

There are many useful techniques for port-site closure, especially when dealing with obese patients, or with large cannula sites through muscle[25–27]. Some other methods are either unnecessarily complicated or unjustifiably expensive, requiring specialized instruments[28,29], some disposable[30]. However, most port sites can be closed safely and effectively using two blunt hooks to lift the corners of the defect, and one small retractor for alternate retraction of the skin edges. The authors have used braided polyglycolic acid or monofilament polyglyconate on a strong 27-mm, 5/8 circular needle (Davis and Geck, St Louis, Missouri, USA) in over 1100 laparoscopic cholecystectomies. The prevention of incisional hernia after laparoscopic cholecystectomy requires an awareness of the various causes, an understanding of the mechanisms involved, and careful observation of sound technique for the insertion, use and removal of ports.

This is a prospective study of the incidence, techniques of access and methods of repair of umbilical and paraumbilical defects encountered in a large series of patients undergoing laparoscopic cholecystectomy. The great majority of umbilical hernias encountered during laparoscopic cholecystectomy can be managed by simple closure of the defect using absorbable sutures.

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Cholecystectomy and fistula closure *versus* enterolithotomy alone in gallstone ileus

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Background The management of gallstone ileus is controversial. This study compared the results of simple enterolithotomy with those of enterolithotomy, cholecystectomy and fistula closure.

Methods A retrospective analysis was made of 25 patients with a mean age of 75 (range 55–84) years. Enterolithotomy was performed in 16 patients (group 1) and cholecystectomy and fistula closure were added in nine patients (group 2).

Results The diagnosis was made before operation in 12 patients, and was associated with previous biliary disorder ($P = 0{\cdot}03$) and pneumobilia ($P < 0{\cdot}001$). Postoperative morbidity occurred in eight patients in group 1 and in six in group 2. Three patients died in each group; all but one of the deaths were unrelated to the surgical procedure. There was no relationship between age and mortality, and patients in American Society of Anesthesiologists (ASA) classes III and IV did not have higher rates of morbidity or mortality than those in ASA classes I and II.

Conclusion Evidence from this study does not support one-stage enterolithotomy, cholecystectomy and fistula closure as the procedure of choice; simple enterolithotomy is appropriate in most patients. However, the one-stage procedure may be acceptable in patients at low risk.

Gallstone ileus is an uncommon condition that may result when a gallbladder or common duct stone enters the intestinal tract, usually as a result of an internal fistula between gallbladder and duodenum, stomach or colon[1–3]. The disorder accounts for only 1–4 per cent of all cases of intestinal obstruction[3–7], but the proportion rises to 25 per cent for non-strangulated obstruction of the small bowel in patients aged over 65 years[4]. Gallstone ileus develops in 0·3–0·5 per cent of all patients with cholelithiasis[5,7,8]. As most patients are 65 years of age or older, the presence of concurrent chronic disorders is common, which could explain the high associated morbidity and mortality rates. Therefore, the most controversial aspect is the proper treatment: enterotomy and removal of the stones alone (simple enterolithotomy) or enterolithotomy in association with cholecystectomy and definitive correction of the internal fistula. If fistula closure is not performed, the patient is prone to several potential complications (recurrent ileus, cholecystitis, cholangitis, gallbladder carcinoma)[4], and many patients refuse a second surgical procedure. As there are few studies in this field, and most of these questions remain unanswered, a review has been made of the authors' modest but relatively important experience of gallstone ileus, bearing in mind the small numbers in many previously published series.

The aim of the study was to assess: (1) morbidity and mortality rates associated with each surgical procedure (enterolithotomy or enterolithotomy, cholecystectomy and fistula closure), and possible advantages of the procedure, if any; and (2) the proportion of cases diagnosed before operation, and the clinical and radiological data required to make a preoperative diagnosis.

Patients and methods

A retrospective analysis was carried out of patients who had gallstone ileus diagnosed between 1975 and 1994 at this hospital. Twenty-six patients were found. In one case the gallstone passed without any sign of intestinal obstruction, so the patient did not require an urgent surgical procedure and was excluded from the study. Therefore, the series consisted of 25 patients (22 women and three men) of mean age 75 (range 55–84) years.

To achieve the previously defined objectives, the following data were obtained. (1) presence of concomitant systemic disease (cardiovascular and neurological disorders, diabetes mellitus, chronic renal failure, chronic obstructive lung disease and malignancy), assessment of operative risk by means of American Society of Anesthesiologists (ASA) physical status classification[9] and factors at the time of surgery that could influence outcome, such as time from symptom onset to operation, shock (systolic arterial blood pressure less than 100 mmHg), and laboratory findings (white blood cell count, haemoglobin, urea, albumin and total protein concentration in serum); (2) antecedents of biliary disease (biliary colic or cholelithiasis diagnosed ultrasonographically; (3) clinical and radiological findings, by re-examination of radiographs (pneumobilia, radiological images suggesting a stone outside the biliary area, delineation of the anatomical extent of the fistula through upper gastrointestinal series), leading to the diagnosis and the time at which the diagnosis was made (preoperative or intraoperative); (4) type of surgical procedure: enterolithotomy (16 patients, group 1) or enterolithotomy, cholecystectomy and fistula closure (nine patients, group 2), selected by the surgeon. The presence of peritonitis, intestinal ischaemia, adhesions around the gallbladder and inflammation was also recorded; (5) early postoperative morbidity (before discharge) – surgical wound abscess, incisional hernia, intestinal or biliary fistula, intra-abdominal abscess, pulmonary, cardiac or renal complications; (6) postoperative death (before discharge); (7) late postoperative morbidity (after discharge and related to the biliary tree) – recurrent gallstone ileus, acute cholecystitis, cholangitis, acute pancreatitis, choledocholithiasis, gallbladder carcinoma.

All but two survivors were followed for a mean of 40 (range 4–96) months. The data were obtained from outpatient office clinical records.

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Statistical analysis

χ^2 test and Fisher's exact test, where appropriate, were used to analyse the effect of qualitative variables on preoperative diagnosis, morbidity and mortality. Analysis of variance was used to study the influence of numerical variables. $P<0{\cdot}05$ was considered significant.

Results

The mean (range) age was 74 (55–84) years in group 1 and 77 (73–80) years in group 2. The difference was not significant. Concurrent disease and ASA grades are shown in *Table 1*. Sixteen patients were affected by one or more systemic disorders, ten in group 1 and six in group 2. Differences in ASA status between the groups were not significant. Data concerning preoperative duration of symptoms together with laboratory and operative findings are given in *Table 2*, which shows similar values for most parameters in both therapeutic groups. There was a significant difference only for inflammation of the gallbladder, which was commoner in group 2. Previous biliary disease was detected in 15 patients: typical biliary pain in five, biliary pain and jaundice in one, cholelithiasis documented by ultrasonography in eight, and cholecystitis, also seen on ultrasonography, in one.

Table 1 Concurrent disease and American Society of Anesthesiologists physical status

	Group 1 ($n=16$)	Group 2 ($n=9$)
Concurrent disease		
Diabetes mellitus	4	0
Hypertension	3	4
Heart failure	2	2
Chronic obstructive lung disease	1	1
Ischaemic heart disease	1	0
Parkinson's disease	0	1
Aortic stenosis	1	0
Lung neoplasm	0	1
Previous parotid tumour	1	0
Gastric neoplasm	0	1
Patients with one or more diseases	10	6
American Society of Anesthesiologists grade		
I	7	1
II	4	2
III	4	5
IV	1	1

Table 2 Patient details

	Group 1 ($n=16$)	Group 2 ($n=9$)	*P*
Age (years)*	74	77	n.s.
Duration of symptoms (days)*	5·5	5·5	n.s.
White blood cell count (cells/ml)*	12 357	13 400	n.s.
Haemoglobin (g/dl)*	14·5	14·5	n.s.
Urea (mg/dl)*	93	67	n.s.
Albumin (g/dl)*	3 1	4 3	n.s.
Shock	2	1	n.s.
Peritonitis	1	1	n.s.
Intestinal ischaemia	2	0	n.s.
Adhesions	11	9	n.s.
Acute inflammation	2	6	0·01†

*Values are mean. n.s., Not significant. †χ^2 and Fisher's exact test

Clinical and radiological picture

Every patient had a typical clinical picture of intestinal obstruction, consisting of crampy abdominal pain, vomiting and abdominal distension. The mean preoperative duration of symptoms was 5·5 days. Physical examination revealed jaundice in two patients. Pneumobilia was seen on abdominal radiography in ten patients and a radio-opaque gallstone outside the biliary area in three. There was complete agreement between the authors' interpretation and that of the operating surgeon. A barium contrast study had been performed in three patients and in every case an upper intestinal obstruction was found; in one the study suggested the existence of an internal fistula, but was not diagnostic. Acute cholecystitis was diagnosed by means of ultrasonography in three cases. Choledocholithiasis was detected only once.

A preoperative diagnosis was obtained in 12 patients and was significantly associated with two variables: antecedents of biliary disease ($P=0{\cdot}03$) and pneumobilia ($P<0{\cdot}001$). Intraoperative diagnosis was made in 13 patients.

Operative findings and surgical procedures

A fistula was identified in nine of the 16 patients in group 1, all of the cholecystoduodenal type; all nine patients in group 2 had a cholecystoduodenal fistula.

Simple enterolithotomy was performed in 16 patients (group 1), although one patient underwent cholecystectomy 4 months later. Enterolithotomy, cholecystectomy and fistula closure was the procedure used in nine patients (group 2).

Postoperative complications and mortality

Early complications and causes of death are shown in *Table 3*. Fourteen patients suffered complications, eight in group 1 (eight complications) and six in group 2 (seven

Table 3 Postoperative complications, reoperations and mortality

	Group 1 ($n=16$)	Group 2 ($n=9$)
Complications		
Wound infection	3	2
Urinary tract infection	2	0
Tachyarrhythmia	0	1*
Aspiration pneumonia	1*	0
Intestinal fistula	0	2*
Systemic sepsis	1*	0
Biliary fistula	0	1
Stroke	1*	0
Undetailed death	0	1*
No. with one or more complications	8	6
Reoperation	0	3
Postoperative mortality	3	3

*Cause of death. There were no significant differences in the rate of complications or mortality between the two groups complications). Three patients, all in group 2, required a second operation: two experienced a new gallstone ileus within 15 days of surgery, and a second enterolithotomy was needed. Another patient underwent reoperation because of leakage of the enterotomy.

Overall, six of the 25 patients died. Three patients died in group 1 as a result of stroke, aspiration pneumonia and systemic sepsis after surgical intervention. Three patients died in group 2 from tachyarrhythmia, peritoneal sepsis due to enterotomy failure and causes poorly detailed in the medical records. Differences in postoperative morbidity and mortality between groups were not significant. Of note, all but one deaths were of medical origin and unrelated to the surgical procedure. No relationship was detected between age and mortality in any group. ASA grades III and IV were not associated with higher rates of morbidity or mortality than ASA grades I and II.

Because acute inflammation in the gallbladder area was significantly more common in patients in group 2, its influence on morbidity and mortality was analysed. Morbidity was slightly higher in group 2 ($P = 0{\cdot}07$) but no relationship was found with mortality ($P = 0{\cdot}27$).

Late complications included one patient in group 1 who developed gallbladder carcinoma 55 months after surgery and died 5 months later; complications in group 2 were acute pancreatitis and transient jaundice, both patients having normal endoscopic retrograde cholangiopancreatographic findings.

Discussion

As the incidence of gallstone ileus is low and the number of conditions with a similar clinical pattern is great, a preoperative diagnosis is obtained in only 50–60 per cent of cases, and is frequently delayed for several days[1–6,10]. The diagnostic rate in the present series was lower, perhaps because of the uncommon use of gastrointestinal contrast radiology. As noted previously, this study confirms the diagnostic value of a history of biliary disease and pneumobilia. Although pre-existing biliary disorders are present in only 20–56 per cent of patients[1,2,6], they must be investigated whenever a condition of unexplained ileus is present, especially when there is no hernia or previous abdominal surgical procedure suggesting adhesions.

Postoperative morbidity and mortality rates are high: the mortality rate ranges from 11·7 to 50 per cent[1,2,11,12] (mean 12·3 per cent[4]), due perhaps to the advanced age of patients[12]. Therefore, treatment is still the main controversial aspect. Simple enterolithotomy has been the classical procedure of choice, but in the past few decades some groups have advocated concomitant definitive correction of the internal fistula to prevent complications such as recurrence of gallstone ileus, cholecystitis, cholangitis, gallbladder carcinoma or malabsorption associated with cholecystocolic fistula[1,6–13]. On the other hand, supporters of simple enterolithotomy adduce the infrequency of recurrent gallstone ileus, the rarity of complications directly related to persistent gallbladder fistula, the possibility of spontaneous closure when there are no residual gallstones[1,2,5,6] and, essentially, the high morbidity and mortality rates that result when definitive correction of the fistula is accomplished[12,14,15]. The collective review of 1001 cases by Reisner and Cohen[4] showed a higher, although not significant, mortality rate (16·9 *versus* 11·7 per cent) in patients undergoing a one-stage procedure. In the present series higher mortality, morbidity and reoperation rates were also found in patients having the one-stage procedure, but again the difference was not statistically significant. It must be borne in mind, first, that many of these patients are in poor general condition and have a delayed diagnosis, frequently leading to dehydration, shock, sepsis or peritonitis, and, second, that the main goal of therapy must be relief of the obstruction and preservation of life. The addition of cholecystectomy and fistula closure can be justified only in selected patients in good condition and able to withstand a more prolonged operation. Delayed cholecystectomy as a second procedure[7,16] is clearly justified only in cases of symptom persistence[4]. In the present patients two cases of recurrent gallstone ileus were noted, which emphasizes the need to examine the whole length of the small and large intestine.

This was not a prospective or randomized study, and the numbers were small, but it involved a considerable number of cases from a single institution of a very uncommon disease, and compared two relatively homogeneous groups according to age and concomitant disease as shown by the ASA classification, laboratory and operative findings. In addition, no relationship was found between ASA status and mortality or morbidity. The only imbalance between groups was the more common presence of gallbladder inflammation (mostly subclinical) in group 2, but this appeared to influence only morbidity, not mortality. Probably it would be wise to leave an inflamed gallbladder, found unexpectedly during operation for gallstone ileus, if there were no preoperative clinical signs of acute cholecystitis, although this could merit further study. Most patients who died had medical complications not related directly to the surgical procedure. Because age did not show any influence on mortality, it might be speculated that general medical condition, possibly not well appreciated by ASA classification, could be a determining factor in the development of postoperative complications.

In view of slightly higher morbidity, mortality and reoperation rates, one-stage enterolithotomy, cholecystectomy and fistula closure cannot be supported as the procedure of choice in gallstone ileus. Therefore, the authors favour enterolithotomy alone in most patients with gallstone ileus, although the one-stage procedure might be acceptable in low-risk patients. It would be necessary to identify clearly (by multicentre studies) low-risk patients who might benefit from a complete one-stage procedure.

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Chemical ablation of the gallbladder

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Background Chemical ablation of the gallbladder might avoid the need for surgery in elderly, unfit patients. This study examined the efficacy of various chemicals in destroying gallbladder mucosa.

Methods Ninety-five per cent ethanol, 3 per cent sodium tetradecyl sulphate (STD), trifluoroacetic acid (TFA) 2 mol/l, tetracycline 50 mg/ml, 30 and 50 per cent phenol, and a mucosal exfoliant solution (compound ethylene diamine tetra-acetic acid) were tested for gallbladder ablation in rabbits. Histology was obtained 8 weeks after exposure to these chemicals.

Results Thirty per cent phenol, tetracycline, TFA and ethanol when used as single agents were moderately effective in causing complete gallbladder mucosal obliteration, 50 per cent phenol caused a macroscopic burn of the entire gallbladder. The mucosal exfoliant solution and STD on their own did not cause mucosal destruction but had significantly enhanced efficacy when combined with 95 per cent ethanol, allowing reliable mucosal destruction with a 5-min contact duration.

Conclusion Ninety-five per cent ethanol and STD after pretreatment with a mucosal exfoliant solution may be the combination of choice for *in situ* gallbladder mucosal ablation.

During *in situ* destruction of the gallbladder as an alternative to cholecystectomy, minimally invasive access to the gallbladder lumen is obtained, gallstones are removed and the mucosa of the gallbladder is destroyed by instillation of chemicals into the lumen of the gallbladder, after occlusion of the cystic duct[1–4]. Theoretically, this should lead to a gallbladder reduced to a shrunken fibrosed remnant incapable of forming further stones. The major attraction of such a procedure is its potential applicability to patients who are unsuitable for general anaesthesia because the gallbladder lumen can be accessed easily under regional anaesthesia[5]. The efficacy of chemicals in common clinical use (in other sites in humans) for *in vivo* ablation of gallbladder mucosa was evaluated in rabbits. Initially a pilot study was conducted with small numbers of animals to identify reagents that were either ineffective or too toxic. These were eliminated from subsequent investigation and the second stage of the study examined chemicals that were safe and effective in more detail.

Materials and methods

All experiments were conducted with the approval of the Home Office. Animals were kept in approved housing and fed a standard diet before and after experimentation. Fifty-five adult female New Zealand White rabbits underwent general anaesthesia with intravenous ketamine/xylazine infusion (induction with intravenous ketamine 70 mg and xylazine 0·02 mg; maintenance with intravenous ketamine 30 mg and xylazine 0·01 mg every 3–5 min as required). A midline laparotomy was performed. The cystic duct was ligated with 4/0 silk. A 23-G intravenous cannula was introduced into the fundus of the gallbladder and bile was aspirated. The gallbladder was then flushed with isotonic saline and an equal volume of saline or the chemical under investigation was instilled into the gallbladder. This was left in contact with the gallbladder mucosa for 5 min and then aspirated. The puncture in the gallbladder was repaired with 4/0 silk suture. The abdomen was closed with continuous 2/0 nylon suture and the skin closed with a subcuticular polyglactin suture. After recovery from the anaesthetic, the rabbits were maintained for 8 weeks. They were then killed by overdose of sodium thiopentone (50 mg/kg by rapid intravenous administration), the abdomen opened and the liver and gallbladder removed and fixed in 40 per cent formaldehyde solution. The gallbladder was cut in slices which were embedded in paraffin, and histological slides were prepared by standard techniques. The tissue was stained with haematoxylin and eosin, and examined by a pathologist who was unaware of the treatment group. The extent of mucosal ablation was graded on a scale of 0–5 (0, obliterated; 5, intact). Complete ablation was defined as total necrosis of gallbladder mucosa with no evidence of regeneration. If any surviving or regenerative mucosa was identified on multiple sections of the gallbladder, the organ was considered to be incompletely ablated. Regenerative mucosa was identified as a single layer of mucosal epithelium. The degree of fibrosis caused by the chemical was also recorded on a similar scale (0, severe fibrosis; 5, no fibrosis). Reagents that were found to be ineffective or toxic in the pilot study were eliminated from further evaluation and a further, more detailed, analysis was carried out of those which were found to be effective (*Table 1*).

Table 1 Chemicals evaluated in the pilot study and second-stage experiments

	No. of rabbits
Pilot study	
Tetracycline 50 mg/ml	3
30% phenol	3
50% phenol	3
95% ethanol+3% STD	3
95% ethanol+TFA 2 mol/l	3
Second-stage experiments	
Saline	5
0·3% STD	5
Stern's solution (mucosal exfoliant solution)	5
95% ethanol	5
95% ethanol+3% STD	10
95% ethanol+3% STD after pretreatment with mucosal exfoliant solution	10

STD, sodium tetradecyl sulphate; TFA, trifluoroacetic acid

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Results

Pilot study

Fifty per cent phenol caused a macroscopic burn on the serosal surface of the rabbit gallbladder at the time of the initial application and full-thickness necrosis of the gallbladder wall on subsequent histology, while all gallbladders exposed to 30 per cent phenol had regenerative potential after 8 weeks (*Table 2*). These chemicals were not studied further. Tetracycline used as a single agent was relatively more effective in ablating mucosa but one of three animals had regenerative mucosa at 8 weeks. Similarly, 95 per cent ethanol with trifluoroacetic acid 2 mol/l caused complete ablation in two of three animals. Ninety-five per cent ethanol plus 0·3 per cent sodium tetradecyl sulphate (STD), on the other hand, caused complete ablation in all three animals (*Fig. 1*) and was therefore subjected to further evaluation.

Table 2 Pilot study for initial evaluation of chemicals

Chemical	*n*	Histology	Comments
95% ethanol+ 3% STD	3	Complete ablation 3 of 3	
95% ethanol+ TFA 2 mol/l	3	Complete ablation 2 of 3	
		Incomplete ablation 1 of 3	Mucocele 1 of 3
Tetracycline 50 mg/ml	3	Complete ablation 2 of 3	
		Incomplete ablation 1 of 3	Mucocele 1 of 3
30% phenol	3	Incomplete ablation 3 of 3	Mucocele 1 of 3
50% phenol	3	Complete ablation 3 of 3	Macroscopic burn at time of application

STD, sodium tetradecyl sulphate; TFA, trifluoroacetic acid

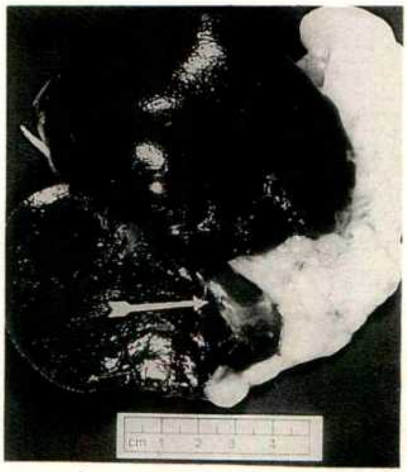

Fig. 1 Macroscopic appearance of ablated rabbit gallbladder. Arrow shows obliterated gallbladder

Second-stage experiments

STD and Stern's exfoliant solution[6] used as single agents did not cause significant mucosal damage but the efficacy of ethanol and STD was significantly enhanced with pretreatment of the mucosa with Stern's solution ($P < 0{\cdot}05$, Fisher's exact test). These results are detailed in *Table 3*.

Discussion

Chemical ablation of the gallbladder as an alternative to cholecystectomy has been under investigation for over a decade[7-11]. There is potential for a minimal access method of *in situ* destruction of the gallbladder without the need for general anaesthesia, which would be especially useful in elderly and unfit patients. The advent of laparoscopic cholecystectomy as a minimal access procedure overshadowed these developments, but it is now becoming

Table 3 Detailed analysis of ethanol, sodium tetradecyl sulphate, mucosal exfoliant and controls (saline)

		Mucosal damage			Fibrosis		
Chemical	*n*	Score*	No. of rabbits	Regenerative potential	Score†	No. of rabbits	Comments
Single agents							
Saline (control) (*Fig. 2*)	5	5	5	Yes	4	2	All animals had mucocele formation
					5	3	
95% ethanol	5	2	1	Yes	2	1	
		1	1	No	1	1	
		0	3	No	0	2	
3% STD	5	4	4	Yes	3	3	Inspissated mucous in gallbladder
		3	1	Yes	2	2	
Stern's solution (compound EDTA mucosal exfoliant)	5	3	2	Yes	3	5	
		2	2	Yes			
		1	1	Yes			
Mixtures							
95% ethano+3% STD	10	0	7	No	2	9	
		1	2	No	4	1	
		2	1	Yes			
95% ethanol+3% STD after pretreatment with Stern's mucosal exfoliant	10	0	9	No	1	10	
		1	1	No			

*Mucosal damage was graded on a scale from 0 (intact) to 5 (obliterated); †degree of fibrosis was scored from 0 (severe) to 5 (none). STD, sodium tetradecyl sulphate

Table 4 Summary of advantages and disadvantages of various chemicals

Chemical	Mechanism of action	Advantages	Disadvantages
Heated contrast medium[7]	Thermal destruction	Visible on fluoroscopy, safe	Not effective
Cyanoacrylate nitrocellulose	Adhesion to tissue	Possible elimination of the need to occlude cystic duct if glue is viscid	Not effective for mucosal ablation
Absolute alcohol and 95% ethanol[8]	Dehydration and denaturation	Safe	Partially effective; prolonged contact may lead to significant absorption
Sodium carbonate[11]	Direct toxicity	Effective	Toxic if leaks out of gallbladder
Tetracycline[9]	Direct toxicity	Safe	Effective only after prolonged contact
Sodium tetradecyl sulphate[12]	Direct toxicity	Safe	Not effective when used alone

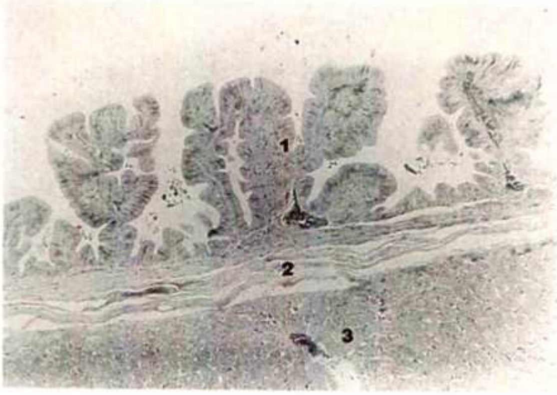

Fig. 2 Histological appearance of normal rabbit gallbladder, showing mucosa (1), muscle (2) and liver (3). (Haematoxylin and eosin stain, original magnification × 400)

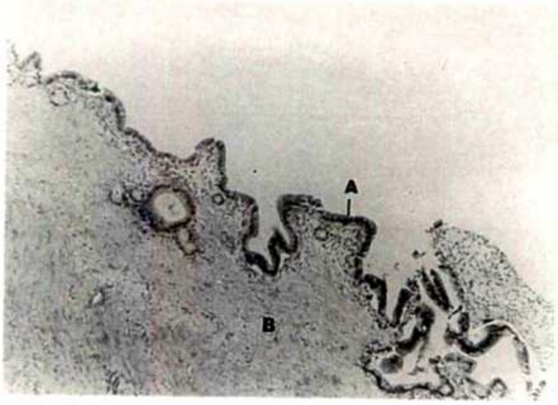

Fig. 3 Histological appearance of partially ablated rabbit gallbladder showing regenerative mucosa (A) and fibrosis (B). (Haematoxylin and eosin stain, original magnification × 400)

clear that the applicability of laparoscopic cholecystectomy is the same as that of open cholecystectomy and that all patients require general anaesthesia.

A suitable chemical for gallbladder mucosal ablation must be safe and effective and require a brief contact time with the mucosa. Previous investigators have evaluated chemicals that are already in clinical use; their advantages and disadvantages are summarized in *Table 4*.

While evaluation of single chemicals determines their individual efficacy, combinations of chemicals are probably more effective in achieving complete mucosal destruction and fibrosis. The present results suggest that tetracycline and 95 per cent ethanol plus STD are effective chemicals for gallbladder mucosal ablation. STD is a commonly used sclerosant in the treatment of varicose veins. On its own it did not ablate the mucosa effectively but caused a fibrotic response; these results confirm the findings of previous investigators who found that with an exposure time of 15 min, STD resulted in no damage to gallbladder mucosa in each of three rabbits at 2 weeks' follow-up[7,9]. At 6 weeks, however, it resulted in complete ablation in only one of five rabbits, with partial or no damage to the mucosa in the remaining four. Ninety-five per cent ethanol has also been evaluated previously[2,7,9,12] and when applied to gallbladder mucosa for 15 min resulted in complete ablation in all of seven rabbits at 2 weeks' follow-up. At 6 weeks' follow-up it resulted in complete ablation in only five of nine rabbits. Increasing the contact time to 30 min, however, resulted in reliable ablation of the mucosa in all eight rabbits at follow-up after 2 and 6 weeks.

The mixture of 95 per cent ethanol and STD appears to be effective (pigs and humans) both at short- and long-term follow-up[2,12]. The combination of 95 per cent ethanol and STD for gallbladder mucosal ablation has not been evaluated previously in rabbits and the present results demonstrate the efficacy of this mixture. However, partial ablation (*Fig. 3*) in two of five rabbits with potential for regeneration shows that the treatment is not invariably effective. The fact that some gallbladders were partially intact implies that this treatment alone may be inadequate for human use. The efficacy of a 5-min exposure to 95 per cent ethanol plus STD after treatment with Stern's solution compares well with the efficacy of tetracycline applied for 30 min to rabbit gallbladder mucosa, i.e. complete mucosal ablation in all of three animals after 6 weeks[9] (*Fig. 4*). The efficacy of tetracycline is reduced with shortened contact time and was much lower for a 15-min exposure time, showing complete ablation in only two of five animals[7]. Whether pretreatment with Stern's solution would increase the efficacy of tetracycline in mucosal ablation with reduced exposure time was not investigated in this study.

Whether increased contact time (up to 30 min) would enhance the efficacy of 95 per cent ethanol and STD was not investigated as it was felt that a short contact time (5 min) was important when considering use of this

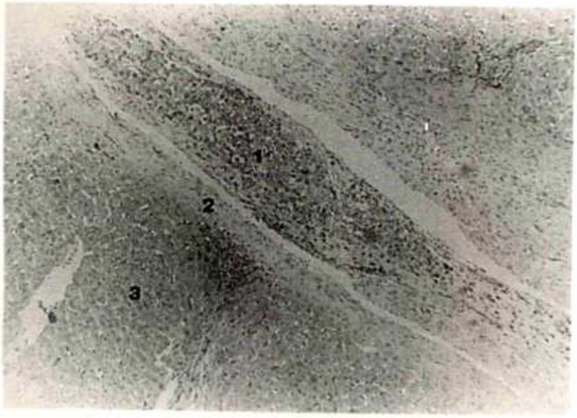

Fig. 4 Histological appearance of completely ablated rabbit gallbladder showing debris (1), fibrous reaction (2) and liver (3). (Haematoxylin and eosin stain, original magnification × 400)

treatment in humans. One of the functions of the gallbladder is to store and concentrate bile in the interdigestive period. Consequently, the surface area of the gallbladder mucosa is large and instillation of chemicals into the gallbladder lumen may result in significant systemic absorption. Remley *et al.*[9] investigated this aspect of chemical ablation and measured serum levels of ethanol, tetracycline and saline (controls) after instillation of these reagents into rabbit gallbladders. Ethanol absorption was measured as a function of contact time with the gallbladder mucosa. Detectable levels of ethanol were present in the serum within 2 min of instillation into the gallbladder and the serum level of ethanol continued to rise until it was aspirated from the gallbladder. Peak serum alcohol levels were 22 mg/dl after 15 min and 46 mg/dl after 30 min of ethanol exposure. Serum concentrations of tetracycline were between 1·6 and 4·6 μg/ml after 30 min. This study demonstrates that absorption of instilled chemicals occurs from the gallbladder lumen although systemic toxicity would depend on the LD_{50} (dose of drug fatal to 50 per cent of a study population) of the instilled chemical.

The optimum duration of follow-up is difficult to establish. The efficacy of these chemicals cannot be quantified against time because all the experiments on mucosal ablation are by nature 'survival' experiments. Some animals show incomplete ablation at shorter follow-up while others show complete ablation at longer follow-up using the same chemical[7]. Whether this is due to an incomplete initial chemical insult or prolonged action of the chemicals is not known. Most studies have followed the animals from 2 to 6 weeks. The size of the rabbit gallbladder precludes multiple sequential biopsies, and even with larger animals (e.g. pigs) the epithelial damage caused by multiple biopsies would probably make the results difficult to interpret.

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Ultrasonographic investigation of the pathogenesis of infusion thrombophlebitis

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Background Thrombophlebitis frequently complicates intravenous infusion, but its precise pathogenesis remains unclear.

Methods Serial B mode ultrasonographic imaging was used to detect intraluminal thrombosis when intravenous nutrition was delivered via fine-bore catheters inserted into peripheral veins.

Results Thrombus was detected in 14 of 22 catheterized veins. There were nine episodes of clinical phlebitis; each was associated with intravenous thrombosis. Venospasm was not observed. The time at which thrombus was first detected varied from within 24 h to more than 15 days after catheterization. Detection of intravenous thrombosis within 24 h of catheter insertion was associated with early catheter complications. Early thrombus tended to be found close to the site of venepuncture, whereas late thrombus was found at the catheter tip, where the hypertonic feed was delivered.

Discussion Ultrasonographic imaging was a useful technique for investigation of infusion thrombophlebitis. Two patterns of thrombosis were observed: distal early thrombosis and proximal late thrombosis. Information acquired may help in the design of novel catheters and strategies to reduce the incidence of thrombophlebitis.

Infusion thrombophlebitis is often trivialized, but may cause substantial discomfort. Occasionally more serious complications develop such as suppuration[1], septicaemia and skin necrosis[2]. Thrombophlebitis is the most important reason why intravenous nutrition (IVN) using a peripheral vein has not gained wider acceptance.

Various factors contribute to the development of thrombophlebitis including catheter or cannula design[3], vein diameter[4], infusion pH[5] and osmolality[6], and duration of infusion[7]. Drugs such as topical glyceryl trinitrate[8], heparin and hydrocortisone[9] reduce morbidity from thrombophlebitis. However, the pathogenesis of infusion thrombophlebitis remains unclear. In a previous study venography was performed via standard intravenous cannulas only after thrombophlebitis had developed[10]. A tourniquet was applied proximal to the cannula which might have affected observations. In particular, it may have accounted for extravasation of contrast. The clinical progression may be rapid[11], and events that occur early in the development of thrombophlebitis may be obscured once clinical signs appear. Intraluminal thrombosis might develop as a consequence of venous inflammation. However, thrombosis might impair blood flow and favour subsequent phlebitis.

This was a prospective study in which catheterized peripheral veins were examined repeatedly by ultrasonography. The phenomena which preceded clinical thrombophlebitis were investigated, without influencing them.

Methods

Patients who received a standard complete nutritional emulsion (1800 kcal, 13 gN, 2500 ml, 1100 mosm/kg)[12] via fine-bore polyurethane catheters (Hydrocath; Ohmeda, Swindon, UK) were studied. Catheters were inserted 15 cm into veins in the antecubital fossa by the Seldinger technique[13], so that the tip lay in a midarm vein. The arm with the most prominent palpable virgin vein was selected. Cannulas were reviewed twice daily and removed at the first symptom or sign of thrombophlebitis[14], or when IVN was no longer required.

A Diasonics Spectra ultrasonographic scanner with a 7·5-MHz transducer (Sonotron, Bedford, UK) was used. Acoustic coupling was maintained with Aquasonic 100 gel (Parker Laboratories, Orange, New Jersey, USA). Catheterized veins were examined between two points. The first was the point at which the catheter entered the vein (insertion site). The second was 15 cm proximal and represented the position of the catheter tip. Intravenous thrombus was detected by visualization of an echogenic mass within the vein lumen, or by failure to obliterate the lumen by pressure with the ultrasonic transducer[15].

When the clinical condition allowed, ultrasonographic examination was performed before catheterization (day 0) and then 24 h later (day 1). Provided that complications did not occur, re-examination was performed on days 7, 10, 15 and 20 after catheterization. If thrombophlebitis intervened, or the patient no longer required IVN, imaging was performed before catheter removal. Patients unfit to leave the ward for examination before catheterization were examined as soon as possible afterwards.

Results

Twenty patients (14 men) of median age 62 (interquartile range (i.q.r.) 50–76) years received 22 fine-bore catheters. Two patients had a second catheter inserted in the contralateral arm (P2b and P7b).

No vein had been subject to recent venepuncture before catheter insertion. Catheters were inserted into veins that had undergone ultrasonographic examination previously on 13 occasions; in each case there was no evidence of thrombosis before catheterization. Nine fine-bore catheters were associated with thrombophlebitis; median time to development was 102 (i.q.r. 83–152) h. Whenever thrombophlebitis occurred, tenderness was greatest at the catheter tip, rather than at the point of venepuncture.

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Intravenous thrombosis

Fourteen catheters were associated with ultrasonographically detected thrombus (*Table 1*). Thrombus was first observed at the point of catheter insertion in three veins (*Fig. 1*), adjacent to the midpart of the catheter in two (*Fig. 2*), and at the catheter tip in nine veins. In six instances thrombus was evident on day 1 ('early' thrombus): in three at the point of insertion, in two in the midvein and in one at the catheter tip. Thrombus first appeared after day 1 (between 6 and 20 days) in eight instances ('late' thrombus), in each case at the catheter tip. When thrombus was first observed at the point of insertion, it had formed within 24 h of venepuncture, whereas in eight of the nine instances in which catheter tip thrombus occurred, thrombus was detected later (between days 6 and 20). Veins were not examined daily by ultrasonography, because access to the vascular laboratory was limited. Therefore, it was not possible to determine exactly when tip thrombus first appeared, but in five cases it was definitely 7 or more days after catheterization.

Table 1 Duration of catheterization, clinical outcome and ultrasonographic observations

Catheter	Duration (h)	Thrombophlebitis	Observations
P1	298	No	No thrombus identified
P2a	154	Yes	Mid-catheter thrombus on day 1
P2b	157	No	No thrombus identified
P3	295	No	No thrombus identified
P4	151	No	Tip thrombus on day 7
P5	102	Yes	Tip thrombus on day 1
P6	466	No	Tip thrombus on day 6
P7a	362	No	No thrombus identified
P7b	264	Yes	Tip thrombus on day 10
P8	79	Yes	Insertion site thrombus on day 1
P9	507	No	Tip thrombus on day 20
P10	405	No	No thrombus identified
P11	93	Yes	Mid-catheter thrombus on day 1
P12	154	No	Tip thrombus on day 10
P13	76	Yes	Insertion site thrombus on day 1
P14	152	No	Insertion site thrombus on day 1
P15	297	Yes	Tip thrombus on day 11
P16	152	No	No thrombus identified
P17	146	Yes	Tip thrombus on day 7
P18	102	Yes	Tip thrombus on day 6
P19	176	No	No thrombus identified
P20	290	No	No thrombus identified

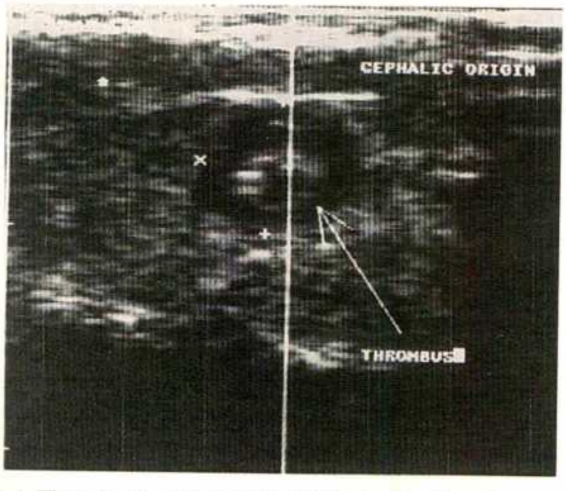

Fig. 1 Thrombosis, at the point of catheter insertion, in cross-section (catheter P8, day 1)

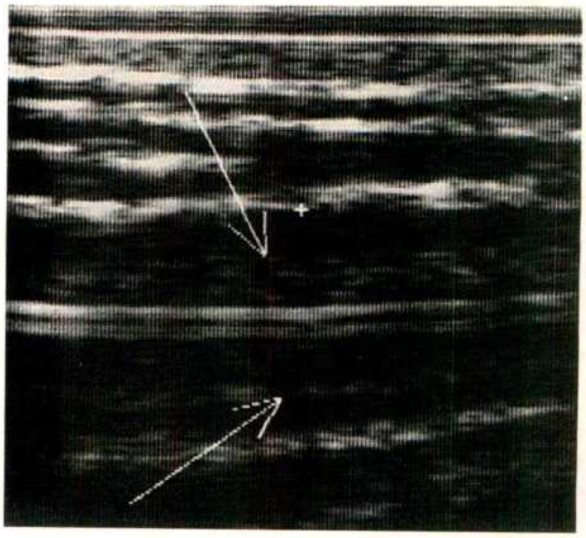

Fig. 2 Thrombosis, at the midpoint of a catheter, in longitudinal section (catheter P2a, day 1)

Thrombophlebitis

Eight catheters, associated with neither ultrasonographically-detected thrombus nor clinical phlebitis, were removed when the patient completed IVN. Of fourteen catheters associated with thrombus, nine were removed because thrombophlebitis developed and five because IVN was no longer required.

Five of six catheters associated with thrombus on day 1 were removed because of subsequent thrombophlebitis; the median time to removal was 93 (i.q.r. 77–100) h. The remaining four episodes of thrombophlebitis occurred at a median time of 205 (i.q.r. 102–264) h, all in veins in which thrombus formed after day 1. Extravasation was not observed during the study.

Discussion

It has been suggested that venoconstriction is the progenitor of thrombophlebitis[16]. The hypothesis was based on animal studies, in which intravenous infusion pressure was measured[17]. Reduced infusion rate and increased infusion pressure were regarded as indicators of venospasm[18]. An alternative explanation is that infusion was impaired by intraluminal thrombosis. Spasm was not observed in any vein in this study. It has been assumed that venous inflammation is the precursor of thrombosis in infusion thrombophlebitis[19]. However, the authors have demonstrated that thrombosis may precede clinical phlebitis by several days. The crucial event in thrombophlebitis is intraluminal thrombosis, secondary to endothelial damage.

Vascular endothelium mediates the balance between intravascular thrombosis and thrombolysis[20], and thrombogenesis is activated by endothelial damage[21]. Intravenous thrombus will reduce blood flow, and dilution of an irritant infusion. Vascular endothelial damage is associated with cell necrosis[22] and reduced endothelial anticoagulant activity[20]. Endothelial abrasion is associated with rapid platelet aggregation[23] which reduces blood flow[24]. Endothelial trauma may lead to complete occlusion of a vein by thrombus. In this study thrombus was observed at sites where endothelial trauma was likely, such as the point of venepuncture or the posterior vein wall where the guidewire, or catheter, could have impacted. Endothelial damage at the catheter tip may have been caused by insertion of the catheter[25,26] or the feed itself. A relationship between degree of intravenous cannula tip deformation and severity of thrombophlebitis has been demonstrated[25]. Catheter movement within the vein[27] might have abraded the endothelium further.

The median time to development of thrombophlebitis in the 'late thrombus' group was twice that in the 'early thrombus' group. Thrombosis at the catheter tip occurred relatively late, probably caused by chemical irritation by the feed. It may have been promoted by shear forces arising from the delivery of feed from the catheter tip, and from acceleration of blood past the catheter[28]. Whenever thrombophlebitis occurred, tenderness was most marked towards the catheter tip, suggesting that inflammation was initiated at the site of feed delivery, rather than at the point of venepuncture. The lifespan of fine-bore catheters, used to deliver bolus antibiotics, can be prolonged by intermittent repositioning so that the infusion does not always impinge upon the same endothelial point[29].

Ultrasonographic imaging to investigate infusion thrombophlebitis was simple, inexpensive and repeatable, and well tolerated by patients. It was non-invasive and enabled investigation without haemodynamic disturbance. Serial examination ensured that the changes which represented thrombosis were new events. Particularly interesting was thrombus detected on day 1, which was associated with early clinical thrombophlebitis. Thrombus is most echogenic in the first 24 h[30,31], so it is unlikely that 'early' thrombosis was overlooked.

Ultrasonographic imaging proved useful for study of the pathogenesis of infusion thrombophlebitis. Thrombosis appeared to be the progenitor of thrombophlebitis. Two patterns were observed: distal 'early' thrombosis, and proximal 'late' thrombosis. Venospasm was not observed but all veins in which clinical thrombophlebitis developed contained thrombus. Although the presence of thrombus *per se* did not predict which catheters would fail before the period of infusion was complete, thrombus detected on day 1 was associated with 'early' thrombophlebitis. The different patterns of thrombophlebitis suggested factors which could be modified to reduce morbidity. Although intraluminal thrombosis may be an unavoidable consequence of venepuncture, improvements in catheter design might reduce endothelial trauma and 'early' thrombosis. Anti-inflammatory agents[9,32] and anticoagulants[9] might reduce 'late' thrombus formation.

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Prospective randomized trial of high-dose bolus *versus* low-dose tissue plasminogen activator infusion in the management of acute limb ischaemia

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Introduction Accelerated thrombolysis with high-dose bolus tissue plasminogen activator (tPA) may enable patients with more severe acute leg ischaemia to be treated without recourse to surgery. This study was a randomized comparison of two thrombolytic regimens.

Methods One hundred patients with acute leg ischaemia of less than 30 days' duration were randomized to receive either high-dose bolus tPA (three doses of 5 mg over 30 min, then 3·5 mg/h for up to 4 h, then 0·5–1·0 mg/h) or conventional low-dose tPA (0·5–1·0 mg/h). The groups were well matched for age, cardiovascular risk factors, duration and severity of ischaemia, site, cause and length of arterial occlusion.

Results The median duration of infusion in the high-dose group was 4·0 (range 0·25–46) h compared with 20 (range 2–46) h for low-dose infusion ($P < 0·0001$). Successful thrombolysis was achieved in 45 of 49 high-dose and 39 of 44 low-dose infusions but significantly more adjunctive procedures were required following high-dose bolus infusion (26 *versus* 16 patients) ($P = 0·002$). Thirty days after treatment was commenced, limb salvage was achieved in 39 of 49 patients in the high-dose group compared with 37 of 44 who had a low-dose infusion of tPA. Six and two patients respectively required amputation. Four patients in the high-dose group and five in the low-dose group died. Three patients in each group suffered a major haemorrhage and one in the low-dose group had a stroke.

Conclusion High-dose bolus therapy significantly accelerated thrombolysis with tPA without compromising outcome. Some 50 per cent of patients were treated within 4 h enabling thrombolysis to be used as primary therapy for patients with acute critical ischaemia.

Intra-arterial thrombolysis has been used as an initial treatment for acute arterial and graft occlusions for over 30 years, but it is only recently that large scientific studies have shown beneficial effects when compared with primary surgery for acute limb ischaemia[1,2]. The majority of intra-arterial infusions in the UK are performed using low-dose techniques which require infusions lasting 20 h or more. Patients with partial or complete neurosensory deficit may not be able to withstand this prolonged period of continued ischaemia and so surgery is frequently required, with its attendant perioperative morbidity and mortality rates. Studies of accelerated thrombolysis using high-dose bolus infusions have reported that the majority of patients can be treated within 4 h[3–5]. The aim of this study was to compare, by a randomized multicentre trial, high-dose bolus infusion of tissue plasminogen activator (tPA) with conventional low-dose tPA infusion in the treatment of acute lower limb arterial ischaemia.

Patients and methods

Patients

Patients over 18 years of age with sudden onset of unilateral acute leg ischaemia (International Society for Cardiovascular Surgery and Society for Vascular Surgery class I·3 or II[6], i.e. incapacitating claudication or rest pain) for whom intra-arterial thrombolysis was considered were eligible for the trial. The duration of symptoms was limited to 30 days for inclusion and both native vessel and graft occlusions were treated. Ischaemia of a severity precluding treatment with low-dose tPA was excluded. Patients were also excluded if thrombolysis was contraindicated because of a recent history (2 months) of stroke, known bleeding diathesis, pregnancy or child bearing age[7].

The protocol was reviewed by the Thrombolysis Study Group and approved by each of the relevant hospital ethics committees. All patients were given verbal and written information about the trial and all gave informed consent. Three hospitals experienced in the technique of peripheral thrombolysis using both high-dose bolus and low-dose infusions participated in the study.

Randomization and treatment protocol

All patients admitted to the participating units with acute limb ischaemia which did not require urgent operation were enrolled. Patients with total limb ischaemia (white leg) who could not withstand further ischaemia had an urgent embolectomy. The remainder were investigated with intra-arterial digital subtraction angiography, usually via the femoral artery of the asymptomatic leg. Angiographic findings were discussed with the responsible vascular surgeon and if intra-arterial thrombolysis was indicated, consent to enter the trial was obtained. At this point patients were assigned to one of the two treatments according to computer-generated randomization cards contained in consecutively numbered, sealed envelopes.

For both treatments, a diagnostic angiocatheter, with an end hole and multiple side holes in the distal 2 cm was embedded in the proximal 2–4 cm of the occlusion, via the puncture site used

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for the diagnostic angiogram. Catheter sizes varied from 3 Fr to 7 Fr in both groups; the commonest was 5 Fr, which was used in 29 of 49 high-dose and 29 of 44 low-dose infusions. Introducer sheaths between 4 Fr and 9 Fr were employed in 36 high-dose and 37 low-dose infusions. In some cases, additional contralateral or direct graft punctures were required. The guidewire was not passed through the entire length of the occlusion but was used to break up the proximal portion of the occlusion. One of the following two treatment protocols was then commenced.

Low-dose tissue plasminogen activator infusion. An infusion into the thrombus via the angiocatheter of 0·5 mg/h or 1 mg/h tPA (0·1 mg in 1 ml of 0·9 per cent saline) was given using a calibrated infusion pump.

High-dose bolus tissue plasminogen activator. Three 5-mg doses of tPA 1 mg/ml were hand injected into the thrombus at intervals of 5–10 min with check angiography through the same catheter after the third injection. If successful lysis was not achieved after the three bolus doses, an infusion of 3·5 mg/h (0·1 mg/ml), using a calibrated infusion pump, was commenced for up to 4 h. If further thrombolysis was required after another angiogram, the infusion rate was reduced to 0·5–1 mg/h.

The method of angiography and technique of catheterization varied slightly between each centre according to local policy; however, within each centre the methods used for the two techniques were the same.

Check angiograms were performed at 4 and 8 h in both groups. If the infusion was continued overnight, angiography was repeated early the following morning. Infusions were terminated when there was evidence of successful thrombolysis, or if there was no change between two angiograms 12 h apart, or if a complication occurred which required cessation of infusion. A completion angiogram was obtained at the end of each infusion. If an underlying lesion amenable to radiological intervention was revealed, angioplasty, atherectomy or suction embolectomy was performed immediately. Some patients required adjunctive surgical procedures within 30 days of the infusions and these were recorded. Adjunctive procedures were conducted according to local policy with standard methods within each centre.

Outcome

Outcome analysis was done using standard definitions developed by the Thrombolysis Study Group[8,9]. Immediate outcome was classified as follows.

Complete lysis was defined as clearance of the occluded vessel with restoration of flow to run-off and re-establishment of peripheral pulses.

Clinically useful lysis was defined as partial clearance of thrombus relieving rest pain or improving ankle:brachial pressure index by 0·2; or partial clearance enabling a smaller operation to be undertaken than was possible before thrombolysis; or partial clearance of thrombus enabling a procedure to be performed, when none was possible before therapy.

Lysis but no run-off or flow was defined as lysis of the acute thrombus without establishing run-off flow into major distal vessels.

Failed lysis was defined as no improvement, or deterioration in the state of limb perfusion.

Additional analysis was performed on the outcome for each patient on the 30th day after treatment: limb salvage (or symptomatic relief in the case of patients presenting with claudication), major amputation (below knee or higher) or death. The total number and type of adjunctive procedures required within 30 days of treatment was noted and the incidence of the following complications recorded: major haemorrhage, completed stroke, compartment syndrome that required fasciotomy, renal failure requiring active intervention, distal embolization resulting in deterioration in condition and/or a change in treatment, rethrombosis and haematoma at the site of arterial puncture affecting management.

Details for each patient, including computerized analysis of angiograms before and after lysis, were recorded prospectively using standard forms that were forwarded to a database coordinator[8]. Computerized angiographic analysis is a novel technique that has been used to divide the distal arterial tree into predetermined anatomical segments. Each can be registered as occluded, patent, stenosed or aneurysmal, and computer software calculates segmental occlusions and run-off scores for sequential angiograms. This has allowed comparison of angiograms for different patients to be made quickly in a standard format[9]. The accuracy of each case report was verified by study monitors who checked the patients' medical records.

Statistical analysis

The primary endpoint was duration of infusion and the secondary endpoint was the incidence of major haemorrhage, defined as bleeding which caused a drop in haemoglobin of 4 g/dl, or required a blood transfusion or an operation for bleeding, or caused death. Categorical data were compared using the χ^2 test; continuous variables were expressed as median values and assessed using the Mann–Whitney statistic.

Results

Patients

One hundred patients were recruited but seven violated the protocol conditions. These patients were considered separately but excluded from analysis. Forty-four patients received low-dose infusions and 49 high-dose bolus therapy with tPA.

There were no significant differences between the demographic details of the two groups, although the median age of the high-dose group was less than that of the low-dose group; 70 (range 54–83) years compared with 73 (range 60–85) years ($P = 0·08$) (*Table 1*). There were no differences between the groups with respect to the site of occlusion and duration, degree or cause of ischaemia (*Tables 2* and *3*). Twenty-two of 49 high-dose bolus infusions were performed for bypass graft occlusions, compared with 17 of 44 low-dose infusions ($P = 0·74$). The majority of grafts were made from polytetrafluoroethylene (PTFE); 13 of 22 and nine of 17 respectively. There were eight *in situ* vein grafts (three and five respectively), four reversed vein grafts (three and one respectively), two composite vein and PTFE grafts (one in each group), and two Dacron (Du Pont, Stevenage, UK) grafts (one in each group). One graft type was unknown. There was no significant difference in graft type between the two groups. Using computerized angio-

Table 1 Demographic data

	High-dose tPA ($n = 49$)	Low-dose tPA ($n = 44$)	P
Median (range) age (years)	70 (54–83)	73 (60–85)	0·08
Sex ratio (M:F)	34:15	27:17	0·42
Diabetes mellitus*	10 (20)	9 (20)	0·99
Ischaemic heart disease*	30 (61)	21 (48)	0·19
Peripheral vascular disease*	37 (76)	34 (77)	0·84
Previous stroke*	3 (6)	3 (7)	0·89
Medication			
Aspirin*	19 (39)	19 (43)	0·82
Warfarin*	7 (14)	6 (14)	0·84

*Values in parentheses are percentages. tPA, tissue plasminogen activator

Table 2 Presenting features

	High-dose tPA ($n = 49$)	Low-dose tPA ($n = 44$)	P
Median (range) duration of ischaemia (h)	96 (12–336)	60 (4–521)	0·55
Incapacitating claudication*	12 (24)	7 (16)	0·46
Ischaemic rest pain*	35 (71)	30 (68)	0·88
Tissue necrosis*	2 (4)	7 (16)	0·25
Audible ankle Doppler signal*	14 (29)	15 (34)	0·57
Partial neurosensory deficit*	27 (55)	19 (43)	0·46
Complete neurosensory deficit*	1 (2)	4 (9)	0·26
Clinical thrombosis*	33 (67)	30 (68)	0·93
Clinical embolus*	8 (16)	13 (30)	0·13
Cause unknown*	8 (16)	1 (2)	0·02

*Values in parentheses are percentages. tPA, tissue plasminogen activator

Table 3 Proximal limit of occlusion

	High-dose tPA ($n = 49$)	Low-dose tPA ($n = 44$)
Native arteries		
Common iliac	0	2
External iliac	1	0
Common femoral	1	2
Proximal superficial femoral	7	7
Distal superficial femoral	4	3
Proximal popliteal	7	7
Distal popliteal	5	4
Tibial vessel	2	2
Grafts		
Above knee femoropopliteal graft	6	2
Below knee femoropopliteal graft	9	9
Femorotibial graft	2	5
Axillobifemoral graft	2	1
Femorofemoral graft	3	0

tPA, tissue plasminogen activator

graphic analysis, the median number of occluded arterial segments before thrombolysis was similar in both groups: 6 (range 2–10) in the high-dose and 7 (range 2–10) in the low-dose group ($P = 0{\cdot}87$).

Duration of infusion

The median duration of infusion in the high-dose bolus group was 4 (range 1–46) h compared with 20 (range 2–46) h for low-dose infusion ($P < 0{\cdot}0001$) (*Fig. 1*). Twenty-five (of the 49) high-dose bolus infusions were completed within 4 h and 32 in 9 h. Only nine of the 44 low-dose infusions were finished within this time.

Immediate outcome

Complete lysis and clinically useful lysis were achieved in a similar proportion of patients in both groups: 22 and 10 of 49 respectively in the high-dose group, and 21 and 14 of 44 respectively in the low-dose group. In the high-dose group 13 infusions resulted in thrombolysis without run-off compared with only four in the low-dose group ($P = 0{\cdot}05$). Computerized angiographic analysis showed that the median number of segments cleared in the high-dose group was 2 (range 0–7) compared with 3 (range 0–5) in the low-dose group ($P = 0{\cdot}12$).

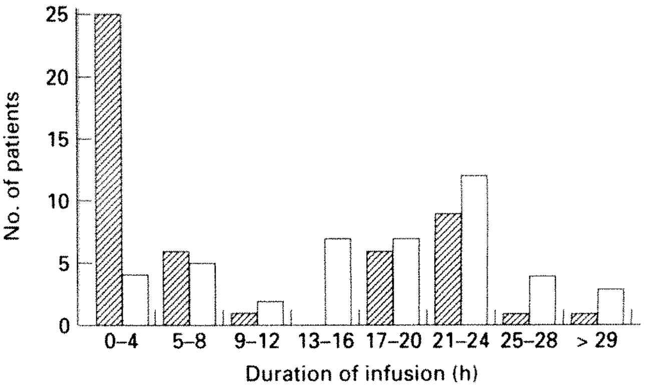

Fig. 1 Duration of infusion for high-dose bolus (▨) and low-dose (□) tissue plasminogen activator infusion

Some 28 stenoses in 18 patients in the high-dose group and 19 stenoses in 16 patients in the low-dose group were revealed by thrombolysis ($P = 0{\cdot}97$). The sites of stenosis were common iliac artery (one in each group), external iliac (one in the high-dose group), superficial femoral artery (11 in high-dose and six in low-dose group), popliteal artery (12 in high-dose and five in low-dose group), tibioperoneal trunk (two in low-dose group), anterior tibial artery (one in each group) and the posterior tibial artery (one in the low-dose group). Five graft stenoses were identified (two in the high- and three in the low-dose group). Four aneurysms, all in the low-dose group, were identified after thrombolysis. The sites were the above knee popliteal artery (one), below knee popliteal artery (two) and at the distal anastomosis of an above knee femoropopliteal PTFE graft (one).

Adjunctive procedures

Patients in the high-dose group had more adjunctive procedures and more vascular reconstructions: 26 compared with only 16 in the low-dose group ($P = 0{\cdot}002$) (*Table 4*). Ten patients in the high-dose group and 11 in the low-dose group required angioplasty alone ($P = 0{\cdot}6$). Sixteen patients in the high-dose group and six in the low-dose group had a combination of procedures ($P = 0{\cdot}04$). Vascular reconstruction was necessary in 11 patients (eight in high-dose and three in low-dose group) because of underlying lesions, failed thrombolysis, distal vessel disease or early rethrombosis.

Thirty-day outcome

The 30-day outcome in the high-dose group was limb salvage in 39 of 49 patients, all of whom had improved symptoms; six required amputation and four died. The causes of death were ischaemic bowel (one), cardiac arrest (one), both within 24 h of starting thrombolysis, myocardial infarction after an upper gastrointestinal bleed 1 week after thrombolysis (one) and renal failure following major haemorrhage (one).

In the low-dose group, limb salvage was achieved in 37 of 44 patients ($P = 0{\cdot}58$) but three had persistent symptoms of rest pain despite surgical intervention. One patient had no effective lysis, then a jump graft and fasciotomy performed but without relief of symptoms. A

Table 4 Procedures performed within 30 days of commencing thrombolysis

	High-dose tPA ($n = 49$)	Low-dose tPA ($n = 44$)	P
Adjunctive procedures*			
Radiological			
Angioplasty	18 (37)	15 (34)	0·79
Atherectomy	4 (8)	0 (0)	0·05
Aspiration embolectomy	2 (4)	1 (2)	0·62
Insertion of arterial stent	0 (0)	1 (2)	0·29
Surgical			
Thromboembolectomy	3 (6)	1 (2)	0·36
Graft reconstruction	8 (16)	3 (7)	0·16
Vein patch angioplasty	1 (2)	0 (0)	0·35
Other procedures†			
Fasciotomy	2 (4)	2 (5)	0·91
Arterial repair	1 (2)	2 (5)	0·49
Major amputation	6 (12)	2 (5)	0·19

Values in parentheses are percentages. *To improve the chance of limb salvage; †for treatment of complications or failed salvage

second patient had lysis but no run-off and had a rethrombosis but refused further intervention. The third patient had a graft thrombosis despite insertion of a jump graft following clinically useful lysis. Only two patients required amputation and five died, three from myocardial infarction at 8, 10 and 20 days after thrombolysis, one from a retroperitoneal haematoma and one from general deterioration after failed lysis. The patient who died from haemorrhage had an urgent arterial exploration after a sheath had become displaced but died later in the intensive care unit despite successful arterial repair.

Complications

There were no statistically significant differences in the number or type of complications encountered in the two groups. Sixteen patients in the high-dose group had complications attributable to thrombolysis and three of these had more than one complication. Three patients had major haemorrhage from the arteriotomy site; one required surgical repair and the others were treated with compression and blood transfusion. Six patients were thought to have suffered from reperfusion injury; two required fasciotomy for compartment syndrome after rapid revascularization and four had abnormal renal function after thrombolysis. Three patients had distal embolization, all of whom improved with continued infusion of tPA. One patient had a groin haematoma which required cessation of the tPA infusion. Other complications included gingival bleeding at the site of a recent dental extraction (one), haematuria 3 weeks after a transurethral resection of prostate (one), minor haemorrhage from an embolectomy wound (one), hypotension which responded to 1 litre of intravenous normal saline (one) and exacerbation of chronic renal failure that was thought to have been induced by radiological contrast agent (one).

In the low-dose group 11 patients suffered from a complication, three of whom had more than one complication. Three patients had major haemorrhage; one died and has been described above, and two required blood transfusion after a puncture-site haemorrhage. One of these patients also had a haemorrhagic stroke while receiving heparin, 36 h after the conclusion of tPA infusion. Two patients suffered distal embolization which improved with continued infusion and one suffered from an occlusion of the 'asymptomatic' leg because of pericatheter thrombosis (heparin was not being administered). One suffered a guidewire perforation of the distal popliteal artery and thrombolysis was then terminated. This subsequently led to an arteriovenous fistula. Two patients required compartment fasciotomy. One patient developed a *Staphylococcus epidermidis* septicaemia after thrombolysis which was thought to be secondary to bacterial contamination of the arterial catheter. One patient developed a PTFE graft infection, possibly secondary to contamination at the time of catheterization, despite antibiotic prophylaxis during thrombolysis.

Patients withdrawn after randomization

Seven patients were withdrawn after randomization because of protocol violations. There were two men and five women of median age 80 (range 47–85) years. Six presented with rest pain and one with claudication, with a median duration of 12 (range 5–821) h. One was withdrawn because the duration of ischaemia was greater than 30 days and another because the presumed graft occlusion was a collapsed but patent vein graft which did not need thrombolysis; the third patient was moribund and had been randomized before consultation with the vascular surgeon. The other four patients received infusions that did not adhere to either the high-dose bolus or low-dose treatment protocols. The immediate outcome for these patients was complete lysis in two, clinically useful lysis in two, lysis but no run-off in two and failed lysis in one. At 30 days four achieved limb salvage and three had died, two from general deterioration and one from pneumonia.

Discussion

This study was not sufficiently powerful to show an advantage in clinical outcome of one technique over the other, but the reduction of infusion time suggests that high-dose bolus therapy may be useful for treating patients with severe acute limb ischaemia rapidly. While only nine of 44 low-dose infusions were completed within one working day, 80 per cent were finished after 24 h (*Fig. 1*). Perhaps some of the patients achieved lysis during an overnight infusion and so may have been exposed to unnecessary hours of tPA infusion with its associated risk of complications. Although the low-dose technique might be improved by increasing the frequency of angiograms conducted 'out of hours' this might be impractical in many centres.

The patient groups were generally well matched, but the high-dose group appeared to have more distal vessel disease which resulted in a significantly higher rate of lysis but no run-off. It may be thought that high-dose therapy did not open run-off vessels as effectively as low-dose infusion, resulting in a higher number of adjunctive procedures, or that there was a higher rate of distal embolization using the accelerated technique. However, the median duration of infusion for patients with lysis but no run-off was 14 h, which was significantly longer than the median of 3 h for other categories ($P = 0·02$). Therefore, infusions which resulted in lysis but no run-off do not seem to have been stopped prematurely, suggesting that the underlying disease was more likely to be the cause rather than embolization or a reduction in the efficacy of infusion.

This study was not powerful enough to detect any significant difference in complication rate or other secondary endpoints. It was encouraging, however, to observe that there was no clinically significant difference in rates of major haemorrhage between the two methods. There was an increase in reperfusion injury, manifesting as compartment syndrome or renal damage, after rapid lysis. This might be expected[10]. Most of the other complications encountered after thrombolysis are well recognized except for the formation of an iatrogenic arteriovenous fistula due to guidewire injury.

High-dose bolus infusion of tPA is of value in the treatment of patients with acute limb ischaemia. The success of the infusion appears to be dependent on the underlying cause of the occlusion which also influences the need for secondary procedures. The technique has the advantage of treating more patients within one working day than conventional low-dose methods.

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Surgical workshop

Safe laparoscopic appendicectomy in suppurative appendicitis

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Intraperitoneal dissection of a suppurating appendix and non-protected extraction through the abdominal wall during laparoscopy may be a source of local contamination. To avoid the risk of infection, evaluation was made of a laparoscopic technique to protect the surgical field from bacteriological spillage as soon as the tip of the appendix has been freed.

Surgical technique

A 3·5 metric endoloop (Ethicon) is passed through the tip of a 10–12-mm cannula, as shown in *Fig. 1*. The thread must be passed from the inside to the outside through one of the two holes located close to the tip of the cannula. The distal extremity of the thread runs outside the sheath, whereas the loop remains locked distally because the knot prevents it from being withdrawn

The cannula is placed above the pubis on the right side under visual control. A 5-mm converter (Multiseal 5 mm; Ethicon) is placed on the cannula and a grasping forceps picks up the tip of the inflamed appendix, which is immediately pulled through the cannula and through the prefixed endoloop. Using bipolar coagulation, the mesoappendix is divided close to the appendix.

As soon as the appendix begins to be freed from its attachments, the grasping forceps is used to pull it gently inside the sheath, avoiding any septic spillage. When the distal extremity of the cannula reaches the caecum, the loop is released on to the appendix base using a hook, and the knot is firmly tightened from the abdomen (*Fig 2*). The tightening process is controlled through the transparent cannula sheath.

The appendix base is reintroduced into the abdominal cavity. The thread is cut 1 cm from the knot, and then the appendix is cut and removed through the cannula without any contact with the abdominal wall. To remove it easily and completely through a cannula remaining in place, care must be taken to open the trocar valve completely and to remove the converter as soon as the appendix glides into the sheath. The rest of the procedure is carried out as usual.

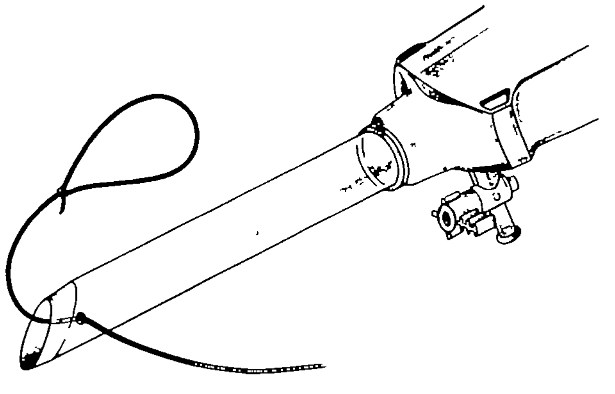

Fig. 1 The thread is passed through a distal hole and the loop positioned around the tip of the cannula

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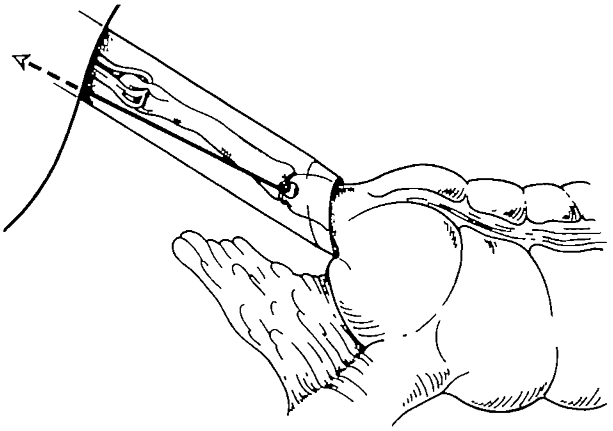

Fig. 2 The knot is tightened on to the appendix base

Thirty patients were operated on (15 men and 15 women of mean(s.d.) age 28·5(16·2) (range 16–83) years). Mean(s.d.) hospital stay was 4·6(1·6) (range 2–8) days. Histological specimens were classified as subacute focal appendicitis in 16 cases, as acute focal appendicitis in two, as suppurative in nine and as chronic appendicitis in three. No complication occurred.

Discussion

This technique decreases the risk of contamination by immediately isolating the appendix. The inflamed appendix may exceed 10 mm in diameter, and so a 12-mm cannula should be used[1–5]. Appendix extraction is occasionally performed through the abdominal wall when the diameter of the cannula is not large enough to let the appendix slide inside the sheath. However, with the present technique the appendix is usually easily hidden inside the sheath. The technique is readily feasible, as rapid as others, safer, and does not require the use of any additional surgical instruments.

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Evaluation of a policy of total mesorectal excision for rectal and rectosigmoid cancers

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Background Total mesorectal excision (TME) is advocated for rectal cancer but the indications and extent of resection vary widely between surgeons.

Methods Seventy-six consecutive patients (61 elective, 15 acute admission) with rectal or rectosigmoid cancer were admitted to a unit where TME was the preferred surgical option for potentially curative cancer at all levels of the rectum.

Results Procedures undertaken were anterior resection (38 patients), abdominoperineal resection (18), Hartmann's procedure (ten) and transanal excision (one). Six patients had proximal faecal diversion alone and surgery was withheld in three. Anastomotic leaks occurred in six of 37 patients who had anterior resection with primary anastomosis, resulting in one early death. The presence of a proximal stoma did not influence the rate or seriousness of anastomotic dehiscence. After potentially curative TME in 45 patients, there have been eight local recurrences, four associated with systemic metastases and four which occurred in isolation (median follow-up 34 months).

Conclusion Curative TME was deemed appropriate in 59 per cent of unselected patients with rectal cancer. It was associated with few local recurrences but a morbidity rate that questions its role in treatment of upper third tumours.

Total mesorectal excision (TME) with sharp dissection of the 'Holy Plane' has been advanced as the 'gold standard' technique for anterior resection of the rectum[1]. It has not always been clear whether this technique has been applied to tumours of the upper third of rectum and rectosigmoid junction for which most surgeons would perform a 'high' anterior resection[2,3]. Recently, Heald and colleagues[4] have reported a preference for treating higher lesions with a less than full rectal excision, transecting the mesorectum 5 cm below the tumour. If the rectum and mesorectum are regarded as a single lymphovascular 'organ' with no internal natural boundaries to the spread of tumour[5], there is some logic in performing a full mesorectal excision for tumours at all levels.

The policy on this unit has been to perform TME in patients with tumours of the middle and lower thirds of the rectum, as part of either anterior resection or abdominoperineal excision of rectum. The preference for upper third tumours, including those at the rectosigmoid junction, has also been for TME, except where incurability or frailty militate against this. This study sought to determine whether TME is practical, is associated with an acceptable level of complications, and is reasonable practice for middle and lower third tumours and selected upper third tumours.

Patients and methods

Between October 1989 and December 1993, 76 (55 male) consecutive patients aged 35–84 (median 68) years with cancers at or below the rectosigmoid junction were admitted.

Examination under anaesthesia was liberally used to assess mobility and to select patients for preoperative radiotherapy. Tumours of the lower and middle thirds of the rectum were treated by low anterior resection as described by Lockhart-Mummery *et al.*[6], using sharp dissection for TME. Where a safe margin of rectal wall beneath the tumour could not be achieved, total anorectal excision was undertaken. The authors' preference for potentially curable upper third tumours was also for low anterior resection with TME. For 'high' anterior resection both the mesorectum and bowel wall were divided 5 cm distal to the tumour. All patients were given prophylactic antibiotics, and the rectal stump was lavaged with aqueous povidone–iodine before constructing the anastomosis.

Curability of resection was defined at laparotomy as 'potentially curative' or 'palliative' (remaining local or distant disease). 'Curability' did not imply clear histological resection margins. All histological sections were reviewed by one consultant histopathologist and tumours staged according to Dukes' 1932 classification[7]: stage A, tumour limited to the wall of the rectum; stage B, tumour extends through the rectal wall into extrarectal tissue; and stage C, lymph node involvement.

Patients were reviewed regularly with clinical examination, sigmoidoscopy and carcinoembryonic antigen assay. Functional outcome was graded using a modified continence scale[8]. Continence scores are: I, perfect control at last follow-up; II, frequency and/or urgency; III, occasional day or night incontinence, slight soiling or the need to wear a pad; IV. total incontinence; and V, failure to close the stoma.

Survival and freedom from local disease were assessed using Kaplan–Meier plots with log rank analysis[9,10].

Results

During the 51-month study period, 76 patients (15 acute admissions) with rectal or rectosigmoid cancer were treated. The American Society of Anesthesiologists (ASA) grades were I–II (55 per cent), III–IV (41 per cent) and unclassified (4 per cent), reflecting a high degree of comorbidity. Tumours were lower third (0–49 mm above anal verge) in 16 patients, middle third (50–99 mm) in 22 patients and upper third/rectosigmoid (100 mm or more) in 29 (*Table 1*). Preoperative examination under anaesthesia ($n = 43$) showed the tumour to be fixed to surrounding tissues in 21 patients. Of these, 19 patients

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received preoperative radiotherapy, one postoperative radiotherapy after Hartmann's resection, and one, with apparent fixity to the vagina alone, abdominoperineal excision of the rectum without radiotherapy.

Colorectal resection was performed in 67 patients (*Table 1*). Anterior resection was performed in 38 (57 per cent), abdominoperineal resection in 18 (27 per cent), Hartmann's resection in ten (15 per cent) and transanal excision of a low rectal cancer in one. Nine patients were unsuitable for colorectal resection, six of whom were given a defunctioning stoma. Fifteen patients admitted acutely underwent the following operations: Hartmann's procedure (four patients), low anterior resection (five), abdominoperineal excision of rectum (one), panproctocolectomy (one), subtotal colectomy with end ileostomy (one) or no resection (three).

Dukes staging[7] for the whole group was stage A ($n = 18$, 25 per cent), B ($n = 24$, 33 per cent), C ($n = 16$, 22 per cent) and extranodal metastases ($n = 14$, 19 per cent); four patients were not staged. Surgery was 'potentially curative' in 50 of 67 patients who underwent tumour excision, and palliative in 17. 'Potentially curative' TME was possible in 45 patients, 28 of 33 low anterior resections, 15 of 18 abdominoperineal resections and two of three Hartmann procedures (*Table 1*).

Anastomotic integrity

Anastomoses were double stapled in 32 of 38 patients undergoing anterior resection (two of which required conversion to a handsewn anastomosis) and handsewn in the remaining six (one colorectal and five coloanal). Anastomotic integrity was assessed by direct inspection and completeness of the doughnuts. In three patients the staple line was found to be disrupted. Two stapled anastomoses were converted to handsewn coloanal anastomoses with covering ileostomies and one was disconnected with creation of an end colostomy. In a further patient with an incomplete doughnut the bowel was simply defunctioned with a loop ileostomy. In all, 20 patients were given a covering loop ileostomy and one an end colostomy at the first operation. In 17 of 33 low anterior resections and four of five high anterior resections the bowel was defunctioned.

Anastomotic leaks were detected after operation in six of 37 patients undergoing anterior resection with primary anastomosis (five clinically and one radiologically). Among patients who had a covering loop ileostomy, four of 20 suffered leakage (three detected clinically and one radiologically), none of whom required immediate operative intervention. This compares with two clinical leaks among 17 patients who had not had the bowel defunctioned, both of whom required laparotomy. Three of 16 patients undergoing low anterior resection with a covering stoma subsequently experienced leakage, compared with two of 16 without a covering ileostomy. One of the high anterior resections (defunctioned because of an incomplete doughnut) suffered a radiological leak.

Table 1 Operative procedure for rectal/rectosigmoid cancer

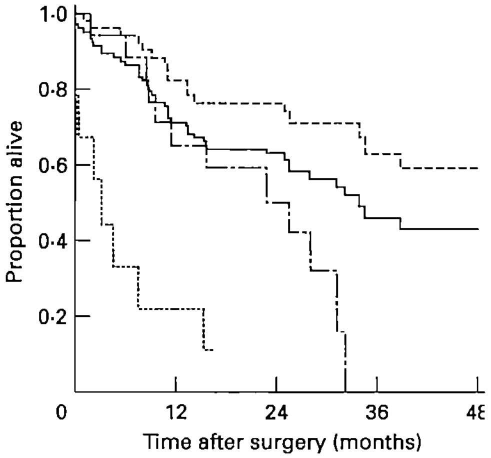
	Tumour level		
	Lower third (<50 mm)	Middle third (50–99 mm)	Upper third (≥100 mm)
APR*	13 (11)	5 (4)	—
Low AR	1 (1)	15 (15)	17 (12)
High AR	—	—	5
Hartmann†	1 (1)	2 (1)	7
Local excision	1	—	—

Tumour level indicates distance between anal verge and lower border of tumour. Values in parentheses are numbers of patients having potentially curative total mesorectal excision. *Includes one panproctocolectomy; †includes one subtotal colectomy and end ileostomy. APR, abdominoperineal excision of the rectum; AR, anterior resection

Anastomotic dehiscence was detected between 19 h (at laparotomy for bleeding) and 30 days after surgery. Three patients had the anastomosis exteriorized, one of whom died with multisystem failure. Only one has subsequently been reanastomosed. Two patients with clinical leaks and one with a radiological leak were managed without operation. Anastomotic stricture developed in four patients, two after documented clinical leaks. Two strictures responded to simple dilatation and one patient died after attempted radiological dilatation leading to perforation. The fourth stricture, which developed after transanal resection of a low rectal tumour, responded to dilatation.

Recurrence rate

The 30-day mortality rate for patients undergoing colorectal resection was one of 66 (2 per cent). Median follow-up was 34 months. Crude actuarial survival at 24 months was 63 per cent (*Fig. 1*). Survival was related to both the surgeon's assessment of curability and Dukes stage (*Figs 1* and *2*). After potentially curative bowel resection ($n = 50$) there have been nine local recurrences, eight after TME (*Table 2*). The actuarial local recurrence rate at 2 years after potentially curative TME was 11 per cent (0, 8 and 30 per cent for Dukes A, B and C



No. at risk					
All patients	76	55	39	16	8
Potentially curative resection	50	41	33	16	8
Palliative resection	17	12	6		
No resection	9	2			

Fig. 1 Crude survival of unselected patients with rectal and rectosigmoid cancer. 'Curability' was judged by the surgeon at or before surgery. ———, All patients; – – –, patients who had potentially curative surgery; —·—·—, patients who had palliative operation; ....., patients who had no resection. $P < 0.001$ (log rank test)

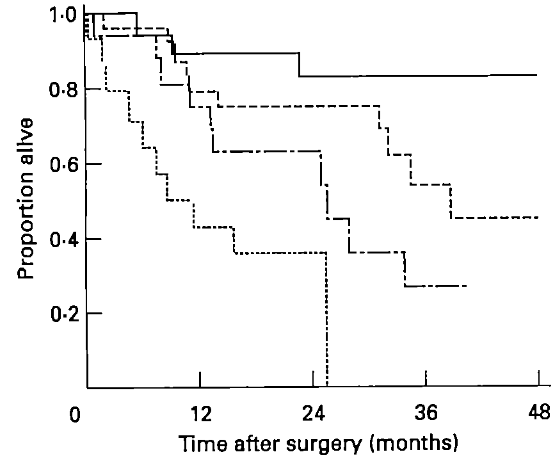
respectively; *Fig. 3*). Four local recurrences have occurred after TME without evidence of systemic relapse (*Table 3*).

Survival and freedom from local relapse were also related to size of the primary tumour (*Figs 4* and *5*). Tumours 50 mm or larger were associated with a poorer prognosis. Short-term outcome did not correlate with tumour grade and distal resection margin.

Functional results

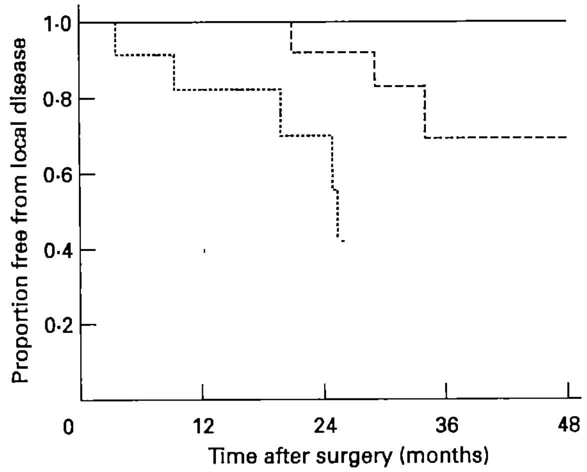
Overall, 56 of 76 patients (74 per cent) received a stoma at the first operation. Late stomas were required in 12 patients (16 per cent) for anastomotic leak (three patients), postoperative pelvic bleeding (three), small bowel perforation (one), incontinence (one) and local recurrence (four).

Postoperative function was assessed clinically in patients who underwent anterior resection. Three patients could not be assessed because of death or short follow-up. Control was perfect (grade I) in 22 of 35 and near perfect (grade II) in eight patients. One patient suffered from occasional incontinence (grade III) and four patients did not have the stoma closed because of anastomotic complications (grade V).



No. at risk					
Dukes A	18	16	15	7	3
Dukes B	24	19	16	6	3
Dukes C	16	12	7	3	
Metastases	14	7	1		

Fig. 2 Influence of disease stage on crude survival. ———, Dukes A; – – –, Dukes B; —·— —, Dukes C; ....., patients with metastases. $P < 0{\cdot}001$ (log rank test)



No. at risk					
Dukes A	14	13	13	6	3
Dukes B	18	16	11	5	3
Dukes C	12	9	5		

Fig. 3 Freedom from local disease of patients undergoing potentially curative total mesorectal excision, according to Dukes stage. ———, Dukes A, ———, Dukes B; ....., Dukes C. $P < 0{\cdot}01$ (log rank test)

Table 2 Local recurrence after potentially curative resection of rectal/rectosigmoid cancer in 50 patients

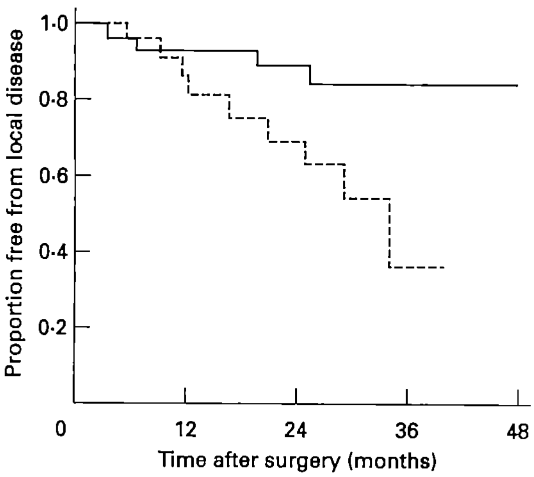
	Tumour level					
	Lower third (<50 mm)		Middle third (50–99 mm)		Upper third (≥100 mm)	
	No. of recurrences	No. at risk	No. of recurrences	No. at risk	No. of recurrences	No. at risk
APR*	2	11	1	4	—	—
Low AR	0	1	2	15	3	12
High AR	—	—	—	—	0	3
Hartmann	0	1	1	2	0	1

Includes 45 patients undergoing potentially curative total mesorectal excision. *Includes one panproctocolectomy. APR, abdominoperineal excision of the rectum; AR, anterior resection

Table 3 Isolated local recurrences after 'potentially curative' total mesorectal excision

Age (years)	Sex	Level (mm)	Size (mm)	Dukes stage	Operation	Time to local recurrence (months)	Outcome
76	M	100	60	C	Low AR	25	Alive at 45 months
54	M	80	50	B	Low AR	21	Dead by 39 months
71	M	90	65	B	APR	29	Alive at 30 months
51	M	25	40	C	APR	3	Dead by 8 months

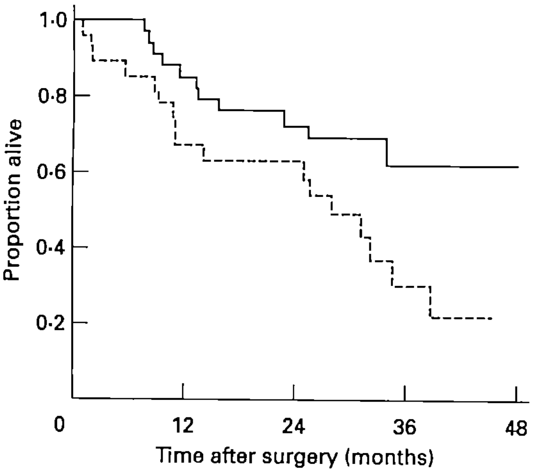
AR, anterior resection; APR, abdominoperineal resection



No. at risk

	0	12	24	36	48
Size < 50 mm	28	25	18	10	6
Size ≥ 50 mm	27	18	12	2	

Fig. 4 Influence of tumour size (———, less than 50 mm; – – –, 50 mm or more) on freedom from local disease after curative or palliative resection of rectal/rectosigmoid tumours. $P < 0·05$ (log rank test)



No. at risk

	0	12	24	36	48
Size < 50 mm	33	29	20	10	6
Size ≥ 50 mm	27	18	15	4	

Fig. 5 Influence of tumour size (———, less than 50 mm; ———, 50 mm or more) on overall survival after curative or palliative resection of rectal/rectosigmoid tumours. $P < 0·05$ (log rank test)

Functional outcome appeared to be unrelated to tumour level, with functional impairment (grade III or more) in three of 14 tumours below 10 cm compared with two of 21 above 10 cm. Of five patients with a coloanal anastomosis, one experienced faecal soiling (grade III) and in one the bowel was defunctioned for incontinence (grade V). Impaired function (grade III or more) was also related to creation of a temporary stoma (5 of 19 patients) compared with primary anastomosis alone (none of 16). Too few patients underwent preoperative radiotherapy with restoration of continuity to know if radiotherapy had any bearing on function.

Discussion

Despite 'potentially curative' surgery for rectal cancer, the number of deaths from colorectal cancer has changed little over the past 50 years[11]. McArdle and Hole[12] showed that 10-year survival after 'potentially curative' resection of colorectal cancer varied between surgeons from 20 to 63 per cent. The 5-year survival rate after R_0 (curative) resection of rectal cancer varies from 40 to 80 per cent depending on the local recurrence rate delivered by the surgeon[13]. The Large Bowel Cancer Project demonstrated variation in local recurrence rates after 'potentially curative' resection for colorectal cancer from less than 5 per cent to greater than 20 per cent, depending on the surgeon[14], and the Glasgow audit[12] demonstrated intersurgeon variation of 0–21 per cent. Although typical local recurrence rates for rectal cancer may be 10–25 per cent[11], individual surgeons have shown that local recurrence rates of 5 and 7 per cent can be achieved, even for Dukes B and C lesions[15,16].

There is growing support for the concept of wide local surgical resection. Published data clearly show that the presence of tumour at the circumferential margin after potentially curative resection is associated with high local relapse rates, with figures of 60 per cent for positive margins *versus* 17 per cent for negative margins reported from Hong Kong[17] and 78 *versus* 10 per cent respectively from Leeds[18]. These data do not prove that achieving clear margins improves the prognosis for individual patients. Lateral margin involvement may merely be a marker of poor prognosis. Dozois and colleagues[19] commented that there are no controlled trials to support the contention that radical surgery diminishes the risk of relapse, but certainly an ill-chosen or poorly executed operation may increase the risk of local recurrence and adversely affect survival. Nevertheless, the use of TME is associated with the lowest local recurrence rate ever reported[20].

This report describes the treatment of rectal and rectosigmoid cancer in an unselected population of patients presenting to a district general hospital in an area where the standardized mortality ratio for many diseases is high. The overall survival for patients with rectal cancer admitted to this unit is disappointing, with 63 per cent alive at 2 years. Only 50 patients (66 per cent) underwent potentially curative surgery, reflecting the large number with fixed tumours or distant metastases. Potentially curative TME was deemed appropriate in only 45 patients (59 per cent), and just over a quarter of these had upper third or rectosigmoid tumours, a controversial indication for TME.

Are the results of TME justifiable? Median follow-up is currently only 34 months but 70–80 per cent of local recurrences occur in the first 2 years[5]. The present local relapse rate (11 per cent) falls within the published range[21] of 3·7–43 per cent but above the 3·7 per cent local recurrence rate reported from Basingstoke[20] although this may be explained partly by the high-risk population in Gateshead. No special assessment was made of microscopic lateral margin involvement. Even resections designated 'potentially curative' were often for large tumours, the importance of which is shown in *Figs 4* and *5*.

The leak rate of 16 per cent (six of 37 patients) among patients undergoing anterior resection is similar to the rate of 17·4 per cent reported from Basingstoke and 18·7 per cent for anterior resection in the Large Bowel Cancer

Project[22]. A high leak rate seems to be an inevitable trade off for trying to achieve optimal local control although the precise reasons for this are not clear. In the present series, a defunctioning stoma did not appear to influence either the leak rate or seriousness of leaks when they occurred. In contrast, Heald[4] found major leaks to be more common (11 of 62 *versus* 13 of 157) and more serious (three deaths *versus* none) in the absence of a proximal stoma.

The functional outcome after TME in this series (18 per cent grade III–IV) mirrors that reported by McAnena and colleagues[8]. Further improvement may be achieved by the use of a colonic J pouch[23].

Many surgeons are persuaded that TME is the gold standard for the surgical treatment of rectal cancer. The excellent results from Basingstoke provide a benchmark which, to date, few surgeons have approached[16,24,25]. The disease characteristics of the authors' catchment population may be responsible for the differences between results in Basingstoke and Gateshead. Nevertheless, there is no room for complacency. Clearly better classification of risk factors, for instance lateral margin involvement, is required in order to dissect out all the confounding variables. The local recurrence rate of 11 per cent together with significant morbidity suggests that there may be little advantage in extending the use of TME to cancers of the upper third of the rectum and rectosigmoid junction. Nevertheless, subgroup analysis is limited by small numbers and the question of best management of lesions of the upper third of the rectum and rectosigmoid requires further study.

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Influence of hospital- and surgeon-related factors on outcome after treatment of rectal cancer with or without preoperative radiotherapy

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Background Preoperative radiotherapy reduces recurrence rates after surgery for rectal cancer but other variables may also affect outcome. The Stockholm Rectal Cancer Study Group has conducted two prospective randomized trials on preoperative radiotherapy in rectal cancer.

Methods This study analysed postoperative morbidity and mortality, local recurrence rate and death from rectal cancer in 1399 patients, according to different hospital- and surgeon-related factors.

Results Patients operated on by surgeons who were certified specialists for at least 10 years had a lower risk of local recurrence (relative risk 0·8 (95 per cent confidence interval (c.i.) 0·6–1·0)) and death from rectal cancer (relative risk 0·8 (95 per cent c.i. 0·7–0·9)). The risk was also lower for patients operated on in university hospitals (relative risk of local recurrence 0·7 (95 per cent c.i. 0·5–0·9), relative risk of death from rectal cancer 0·8 (95 per cent c.i. 0·7–1·0)) compared with community hospitals, although the results in some community hospitals were similar to those in university hospitals. The proportional reduction of local recurrence rate after preoperative radiotherapy was not significantly different for the studied institutions and surgeons.

Conclusion There was a significant surgeon-related variation in patient outcome, which is probably related to the surgical technique. Although improved technique may reduce the local recurrence rate, preoperative radiotherapy is still beneficial concerning local control and survival.

Considerable surgeon-related variability in patient outcome after surgery for colorectal cancer has been reported in previous studies[1,2]. The surgeon seems to be an independent prognostic factor, influencing the extent of postoperative morbidity and mortality, local recurrence rate and overall survival. These variations in outcome have been explained by differences in surgical technique[1,3,4].

Differences in local recurrence rate after potentially curative surgery may be explained partly by differences in individual surgical skill[4]. In addition, the local recurrence rate is related to overall survival, so surgical skill may have an impact on survival[2].

Preoperative radiotherapy reduces the risk of local recurrence in rectal cancer[5–8]. However, the local failure rate in irradiated patients, as presented in different trials, still seems to be higher than results presented by individual surgeons using total mesorectal excision without adjuvant therapy[9–11].

Although it has been postulated that the proportional reduction in local recurrence rate after preoperative radiotherapy might be at least as high in connection with 'optimized' surgery, as it is when combined with 'standard' surgery, there are no published data to support this hypothesis[12].

The present study was based on 1399 patients included in two Swedish prospective randomized trials of preoperative radiotherapy in rectal cancer. It analyses the effects of hospital- and surgeon-related factors on postoperative morbidity and mortality, local recurrence rate and survival. The aim was to assess the impact of the treating hospital and surgeon on the outcome after rectal cancer surgery and to analyse whether the relative reduction in local recurrence rate after preoperative radiotherapy was similar in different hospitals and for different surgeons.

Patients and methods

In 1980 the Stockholm Rectal Cancer Study Group initiated a prospective randomized trial of preoperative radiotherapy in rectal cancer (the Stockholm I Trial). Patients with biopsy-proven rectal adenocarcinoma living in the County of Stockholm, on the Island of Gotland or in the City of Malmo were eligible. Patients were stratified according to treatment centre and randomized to radiotherapy followed by surgery or to surgery alone. Those allocated to preoperative radiotherapy received a total dose of 25 Gy, in five fractions over 1 week, and surgery was performed within 1 week thereafter. Irradiation was given with a two-portal technique to a large volume including the anus, rectum, perirectal tissues, perineum and regional lymph nodes up to the level of the second lumbar vertebra[13]. Until February 1987 the trial included 849 patients. During follow-up a significant reduction in the local recurrence rate was observed in patients given radiotherapy but there was also an increased postoperative mortality (within 30 days) in irradiated compared with non-irradiated patients (8 *versus* 2 per cent). This increased postoperative mortality rate resulted mainly from a higher risk of cardiovascular death in elderly patients after radiotherapy. Details and results of the study have been published previously[7,14,15].

In an attempt to reduce the postoperative mortality rate with a maintained reduction in the local recurrence rate after radiotherapy, the study protocol was changed in 1987 (the Stockholm II Trial). Radiotherapy was given with a four-field technique to a reduced volume and patients older than 79 years were excluded. This study included patients living in the County of Stockholm and on the Island of Gotland. The Stockholm II Trial closed in May 1993, when 557 patients had been included. The local recurrence rate was reduced and patient survival improved after preoperative radiotherapy, but there was no significant increase in the postoperative mortality rate in irradiated compared with non-irradiated patients (2 *versus* 1 per cent)[16].

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Design of the present study

Data on postoperative complications including mortality, the dates of reported local or distant recurrence, and the cause of death were prospectively registered at the study secretariat Follow-up data on all patients were available until January 1995, the median follow-up time in the Stockholm I Trial was then 140 (range 95–178) months and in the Stockholm II Trial 62 (range 19–95) months

Postoperative complications related to the surgical technique were analysed. Wound infection, wound dehiscence and anastomotic leakage were thus classified as surgical complications

Patient outcome, in terms of postoperative mortality (within 30 days of surgery), surgical complications and survival, was analysed in all patients, while local recurrence was analysed only in those operated on for cure. Surgery was defined as curative if the surgeon reported complete resection of the primary tumour and no distant metastases, and the pathologist reported tumour-free margins of the specimen

All patient data were analysed according to the allocated treatment (i.e. preoperative radiotherapy), regardless of whether the patient actually received that treatment In all, 14 hospitals participated in the trials. They randomized a total of 1406 patients, 1399 of whom had surgery and were included in the present study. Of these, 1175 patients were operated on with curative intent Eleven hospitals participated in both trials, two hospitals participated only in the first trial and one hospital only in the second. Three hospitals were university hospitals, i e. formal educational institutions with chairs in surgery, associated with the local university faculty of medicine. Two hospitals were large community hospitals that also educated medical students. Nine hospitals were community hospitals of variable size, without formal education of medical students. All 14 hospitals included surgeons in training, i e not board-certified or equivalent grade.

To assess the relationship between outcome and hospital volume, the hospitals were classified according to the annual mean number of patients included in the studies who had rectal cancer operations during the study period· hospitals averaging 5 patients or fewer each year; hospitals averaging 6–10 patients yearly; and hospitals averaging more than 10 patients per year. The three groups of hospitals were compared according to patient outcome after surgery, defined as postoperative mortality or surgical complications, local recurrence and death from rectal cancer A similar comparison was also made between the three university hospitals and 11 non-university hospitals. In 1372 patients the operation notes were reviewed and the operating surgeon was recorded and given a specific code. When two or more surgeons participated at the operation, the senior surgeon was regarded as the operating surgeon In 27 patients the operation notes could not be retrieved.

During the course of the trials, some surgeons retired or moved to other areas in Sweden, while others were appointed at the participating hospitals To estimate the mean annual number of rectal cancer operations performed by each surgeon, the total number of patients operated on by the surgeon was divided by the number of years he or she had contributed patients to the trials To study the effect of surgeon volume on outcome, surgeons were divided into two categories 1–3 operations per year and more than 3 operations per year.

The date of the equivalent to board-certification for each surgeon was available from The National Swedish Board of Health and Welfare. The time between that date and the date of surgery was calculated for each patient. This 'time as a specialist surgeon' was divided into two categories, 10 years or fewer and more than 10 years, and analysed in relation to patient outcome

To estimate the between-hospital variability, results were also analysed separately for each hospital. The between-surgeon variability was assessed by comparing the outcome for patients operated on by 11 different surgeons who each had performed a total of more than 25 rectal cancer operations within the trials

Statistical analysis

Postoperative mortality and surgical complications according to hospital- and surgeon-related variables were analysed using a logistic regression model. Comparisons of cumulative incidence of local recurrence and patient survival were made using a Cox proportional hazards model In the multivariate analyses adjustment was made for age, sex, Dukes stage and radiotherapy treatment

Results

Data on the total number of rectal cancer operations, mean number of operations per year, type of surgery performed, number of curative operations and number of operating surgeons for each hospital are given in *Table 1*. The mean annual number of operations per hospital varied between 4 and 19. The proportion of abdominoperineal resections varied between 46 and 69 per cent, and curative surgery was performed in 77–91 per cent of the patients. In all, 149 different operating surgeons were recorded and the total number of rectal cancer operations performed by each during the study period varied

Table 1 Selected characteristics of hospitals participating in the two Stockholm trials

Hospital no.	No. of patients	Mean (range) patients per year	Anterior resections*	Abdominoperineal resections*	Other surgery*†	Curative surgery*	No. of surgeons
1	119	9 (2–14)	53 (45)	59 (50)	7 (6)	101 (85)	17
2	57	5 (2–13)	19 (33)	32 (56)	6 (11)	44 (77)	12
3	66	13 (9–17)	19 (29)	37 (56)	10 (15)	53 (80)	11
4	221	16 (4–29)	75 (34)	139 (63)	7 (3)	192 (87)	16
5	140	10 (4–14)	66 (47)	72 (51)	2 (2)	116 (83)	12
6	147	11 (2–20)	72 (49)	71 (48)	4 (3)	127 (86)	14
7	63	11 (1–16)	22 (35)	40 (63)	1 (2)	54 (86)	12
8	184	13 (4–18)	57 (31)	110 (60)	17 (9)	147 (80)	19
9	55	6 (2–9)	23 (42)	28 (51)	4 (7)	47 (85)	9
10	49	4 (1–8)	11 (22)	33 (67)	5 (10)	38 (78)	5
11	52	4 (2–8)	14 (27)	36 (69)	2 (4)	43 (83)	7
12	81	7 (1–12)	27 (33)	46 (57)	8 (10)	65 (80)	9
13	70	6 (1–10)	22 (31)	45 (64)	3 (4)	64 (91)	15
14	95	19 (3–30)	48 (51)	44 (46)	3 (3)	84 (88)	11
Total	1399	100 (30–158)	528 (38)	792 (57)	79 (6)	1175 (84)	169‡

*Values in parentheses are percentages. †Includes exploratory laparotomy, local excision and Hartmann's procedure ‡Twenty surgeons performed operations in more than one hospital between one and 87. Eighty surgeons performed fewer than six operations, 25 did six to ten, 19 did 11–15, ten 16–20, four 21–25 and 11 surgeons performed more than 25 operations. The mean annual number of operations performed by each surgeon varied between 1 and 9. Only nine surgeons averaged more than 3 rectal cancer operations per year

Table 2 shows the number of postoperative deaths, surgical complications, local recurrences and deaths from rectal cancer among the patients who underwent surgery, according to the studied hospital- and surgeon-related parameters. Adjusted odds and hazard ratios for the studied endpoints are listed in *Table 3*.

Hospital-related prognostic factors

The risk of postoperative deaths and surgical complications appeared to decrease with increasing number of rectal cancer operations performed in each hospital, but the differences were not significant. The type of hospital did not influence the postoperative mortality or surgical complication rate.

The crude local recurrence rate was 26 per cent in hospitals averaging fewer than 5 operations per year and 20 per cent in those which performed more than 10 rectal cancer operations annually. This difference was of borderline significance ($P = 0·06$).

In non-university hospitals the crude local recurrence rate was 23 per cent compared with 17 per cent in university hospitals. This risk reduction for local recurrence in patients who had surgery in university hospitals was significant (relative risk 0·7 (95 per cent confidence interval (c.i.) 0·5–0·9)) after adjustment for other prognostic factors. Similarly, patients who had surgery in university hospitals had a lower risk of death from rectal cancer than those from non-university hospitals (relative

Table 2 Curative surgery, postoperative mortality and surgical complications, local recurrence and deaths from rectal cancer according to hospital- and surgeon-related variables

	No. of patients	Curative surgery	Postoperative mortality	Surgical complications	Local recurrence*	Deaths from rectal cancer
Hospital variables						
Mean no of operations per year						
≤5	158	125 (79)	7 (4·4)	32 (20)	33 (26)	84 (53)
6–10	465	393 (85)	18 (3·9)	91 (20)	91 (23)	221 (48)
>10	776	657 (85)	26 (3·4)	141 (18)	132 (20)	362 (47)
Non-university hospital	1094	910 (83)	42 (3·8)	197 (18)	212 (23)	539 (49)
University hospital	305	265 (87)	9 (3·0)	67 (22)	44 (17)	128 (42)
Surgeon variables						
Years as specialist surgeon						
≤10	467	381 (82)	23 (4·9)	92 (20)	95 (25)	248 (53)
>10	857	737 (86)	24 (2·8)	154 (18)	150 (20)	379 (44)
Missing data	75					
Mean no of operations per year						
1–3	1037	863 (83)	37 (3·6)	206 (20)	197 (23)	505 (49)
>3	335	294 (88)	13 (3·9)	54 (16)	58 (20)	149 (44)
Missing data	27					

Values in parentheses are percentages. *After curative surgery

Table 3 Adjusted odds and hazard ratios of postoperative mortality and surgical complications, local recurrence and rectal cancer deaths according to hospital- and surgeon-related variables

	Adjusted odds ratio		Adjusted hazard ratio	
	Postoperative mortality	Surgical complications	Local recurrence	Deaths from rectal cancer
Hospital variables				
Mean no of operations per year				
≤5	1·0	1·0	1·0	1·0
6–10	0·9 (0·3–2·3)	0·9 (0·6–1·5)	0·9 (0·6–1·4)	1·0 (0·8–1·3)
>10	0·7 (0·3–1·8)	0·8 (0·5–1·3)	0·7 (0·5–1·1)	0·9 (0·7–1·1)
Non-university hospital	1·0	1·0	1·0	1·0
University hospital	0·8 (0·4–1·7)	1·3 (0·9–1·7)	0·7 (0·5–0·9)	0·8 (0·7–1·0)
Surgeon variables				
Years as specialist surgeon				
≤10 years	1·0	1·0	1·0	1·0
>10 years	0·6 (0·4–1·2)	0·9 (0·6–1·2)	0·8 (0·6–1·0)	0·8 (0·7–0·9)
Mean no. of operations per year				
1–3	1·0	1·0	1·0	1·0
>3	1·2 (0·6–2·3)	0·7 (0·5–1·0)	0·9 (0·7–1·2)	0·9 (0·7–1·1)

Values in parentheses are 95 per cent confidence intervals. Odds and hazard ratios are adjusted for age, sex, Dukes stage and radiotherapy treatment risk 0·8 (95 per cent c.i. 0·7–1·0)). The mean annual number of rectal cancer operations performed in each hospital was not related to rectal cancer mortality rate.

Surgeon-related prognostic factors

The risk of postoperative death and surgical complications were not significantly related to the surgeon's experience, nor to the mean annual number of rectal cancer operations performed by the surgeon. Patients operated on by surgeons with more than 10 years as a specialist had a lower local recurrence rate (relative risk 0·8 (95 per cent c.i. 0·6–1·0)) after adjustment for other prognostic factors. The risk of death from rectal cancer was also significantly lower in patients operated on by experienced surgeons (relative risk 0·8 (95 per cent c.i. 0·7–0·9)). The mean annual number of operations performed by the operating surgeons did not significantly influence the risk of local recurrence or death from rectal cancer.

In university hospitals, 225 (74 per cent) of 305 patients had operations by surgeons with more than 10 years as a specialist; the corresponding figures in non-university hospitals were 632 (58 per cent) of 1094. To adjust for this imbalance, surgeon experience was introduced in the multivariate analysis in addition to age, sex, Dukes stage and radiotherapy. After this adjustment there was still a reduced risk of local recurrence (relative risk 0·7 (95 per cent c.i. 0·5–1·0)) and death from rectal cancer (relative risk 0·8 (95 per cent c.i. 0·7–1·0)) in patients operated on in university hospitals. Similarly, after adjustment for university or non-university hospital, patients operated on by surgeons with more than 10 years as a specialist had a lower risk of local recurrence (relative risk 0·8 (95 per cent c.i. 0·6–1·0)) and death from rectal cancer (relative risk 0·8 (95 per cent c.i. 0·7–1·0)).

Between-hospital variability

Results for individual hospitals are listed in *Table 4*. Each hospital was compared with the 13 others combined (risk ratio 1). Relative risk ratios were calculated after adjustment for other prognostic factors, as shown in *Fig. 1*. The adjusted relative risk for postoperative mortality or surgical complications varied between hospitals from 0·5 to 1·7, for local recurrence from 0·4 to 2·0 and for death from rectal cancer from 0·6 to 1·9. However, the heterogeneity between hospitals was not statistically significant for any of these events.

Table 4 Comparison of postoperative mortality and surgical complications, crude local recurrence rate and crude incidence of death from rectal cancer for each hospital

Hospital no.	No. of patients	Postoperative deaths or surgical complications	Patients with local recurrence	3-year cumulative incidence of local recurrence (%)	Deaths from rectal cancer	5-year cumulative incidence of death from rectal cancer (%)
1	119	30 (25)	32	32	47	49
2	57	14 (25)	11	28	25	56
3	66	15 (23)	11	25	24	47
4	221	31 (14)	48	24	78	37
5	140	29 (21)	21	17	34	29
6	147	35 (24)	22	15	49	38
7	63	12 (19)	11	20	19	37
8	184	39 (21)	29	19	60	45
9	55	8 (15)	12	27	26	54
10	49	15 (31)	14	27	16	43
11	52	9 (17)	8	16	13	37
12	81	15 (19)	12	13	22	32
13	70	19 (27)	13	19	27	41
14	95	29 (31)	11	13	26	32

Values in parentheses are percentages. Local recurrence and death from rectal cancer were analysed only in patients who had curative surgery

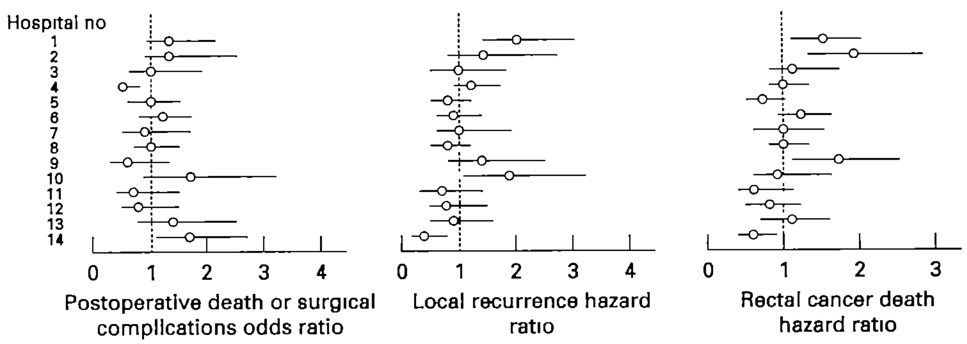


Fig. 1 Patient outcome analysed separately for each hospital participating in the Stockholm trials. Each hospital was compared with all the other hospitals combined (relative risk 1). Odds and hazard ratios were adjusted for age, sex, Dukes stage and radiotherapy The 95 per cent confidence interval is indicated by bars. A test for heterogeneity gave $P = 0{\cdot}1$ in each case

Table 5 Comparison of operative method and outcome in patients operated on by surgeons who performed more than 25 rectal cancer operations within the two Stockholm trials

Surgeon no	No. of patients	Abdomino-perineal resections (%)	Anterior resections (%)	Post-operative deaths	Surgical complications	Patients with local recurrence	3-year cumulative incidence of local recurrence (%)	Death from rectal cancer	5-year cumulative incidence of death from rectal cancer (%)
1	87	83	16	1 (1)	9 (10)	15	20	23	34
2	25	46	54	0 (0)	4 (16)	7	29	10	40
3	71	53	47	3 (4)	7 (10)	19	26	32	36
4	28	39	52	3 (11)	4 (14)	6	28	10	41
5	62	47	51	3 (5)	14 (23)	8	11	23	41
6	31	44	56	5 (16)	6 (19)	12	41	12	57
7	42	61	36	1 (2)	8 (19)	7	15	15	54
8	30	77	23	0 (0)	5 (17)	0	0	4	17
9	26	43	57	1 (4)	5 (19)	2	11	5	16
10	27	50	50	0 (0)	4 (15)	0	0	5	32
11	35	55	45	1 (3)	14 (40)	3	7	9	33

Values in parentheses are percentages. Local recurrence and death from rectal cancer were analysed only in patients who had curative surgery

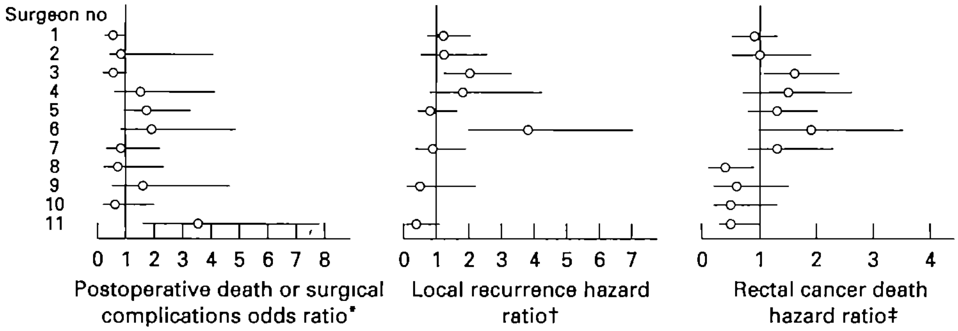


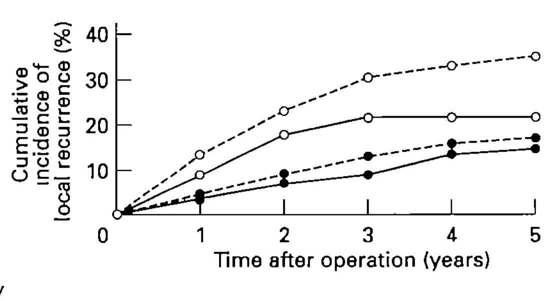
Fig. 2 Comparison of results between 11 surgeons who each performed more than 25 rectal cancer operations within the Stockholm trials. Each surgeon was compared with all the other surgeons combined (relative risk 1) The 95 per cent confidence interval is indicated by bars. Local recurrence hazard ratio could not be estimated for surgeons 8 and 10, since no local recurrence was observed in their patients *$P = 0{\cdot}01$, †$P < 0{\cdot}001$, ‡$P = 0{\cdot}04$ (test for heterogeneity)

Between-surgeon variability

Eleven surgeons performed more than 25 rectal cancer operations each within the Stockholm trials. Patients operated on by these surgeons were analysed regarding type of surgery, postoperative mortality or surgical complications, local recurrence rate and death from rectal cancer (*Table 5*). There was considerable between-surgeon variation in the proportion of abdominoperineal resections (39–83 per cent), in postoperative death or surgical complications (10–40 per cent for the latter), in the 3-year cumulative incidence of local recurrence (0–41 per cent) and in the 5-year cumulative incidence of death from rectal cancer (16–57 per cent). The results for each surgeon were compared with the results for all the other surgeons combined and odds or hazard ratios calculated after adjustment for age, sex, tumour stage and radiotherapy. The heterogeneity between surgeons was significant for the three studied endpoints (*Fig. 2*). The lower local recurrence rate and lower percentage of deaths from rectal cancer for some surgeons were not explained by an increased postoperative mortality (data not shown).

Radiotherapy

The overall risk of local recurrence was reduced by a factor of 0·5 (95 per cent c.i. 0·4–0·6) after preoperative radiotherapy, compared with surgery alone. In non-university hospitals the crude local recurrence rate was 32 per cent after surgery alone and 14 per cent after preoperative radiotherapy with surgery. The corresponding figures in university hospitals were 18 and 13 per cent



No at risk	0	1	2	3	4	5
University						
Radiotherapy	126	108	98	88	73	61
No radiotherapy	139	118	96	79	68	53
Non-university						
Radiotherapy	444	359	309	251	211	178
No radiotherapy	466	383	303	232	184	152

Fig. 3 Cumulative incidence of local recurrence in university and non-university hospitals, according to allocated treatment. University hospitals· —●—, radiotherapy, —○—, no radiotherapy. Non-university hospitals: – –●– –, radiotherapy; – –○– –, no radiotherapy

respectively. The cumulative incidence of local recurrence in university and non-university hospitals according to allocated treatment is shown in *Fig. 3*. Preoperative radiotherapy reduced the risk of local recurrence by a factor of 0·4 (95 per cent c.i. 0·3–0·6) in non-university hospitals and by 0·8 (95 per cent c.i. 0·4–1·4) in university hospitals. However, a test of interaction between preoperative radiotherapy and university or non-university hospital was not significant ($P = 0{\cdot}16$), i.e. the hypothesis that radiotherapy reduced the risk of local recurrence similarly in both types of hospitals could not be rejected. Similarly, the proportional reduction in the local recurrence rate after irradiation was not significantly different for the 11 surgeons analysed separately (data not shown).

Discussion

Comparison of patient outcome by hospital- and surgeon-related factors is difficult and remains controversial. Studies of gynaecological malignancy, breast cancer and gastric cancer indicate that surgeon subspecialization improves treatment results[17–19]. This has also been suggested for colorectal cancer[20,21].

Different studies in rectal cancer have claimed that the individual surgeon is an independent prognostic factor, influencing the risk of postoperative mortality and morbidity, local recurrence rate and survival[1,2,4]. Although differences in patient outcome between individual surgeons are well established, the reasons for this variation are unclear[1].

Meticulous attention to surgical detail has been proposed as one explanation, but there is no evidence to indicate which technical aspects are more important[4]. Complete excision of the mesorectum is associated with a low rate of local recurrence, also without adjuvant radiotherapy[11,22,23]. This could be one example of the importance of precise surgical technique with regard to outcome. In Sweden there is no specific board-certification for colorectal surgeons. Thus, most general surgeons perform colorectal cancer surgery, although there has been a tendency towards colorectal subspecialization in recent years, at least in the larger hospitals. Most surgeons who operated on patients with rectal cancer in the Stockholm trials were not subspecialized in colorectal surgery and performed few rectal cancer operations. In addition, the majority of surgeons did not adopt the total mesorectal excision technique as described by Heald. Blunt dissection was used in most patients and the operation notes did not usually reveal the extent of mesorectal excision or details on preservation of presacral nerves.

As differences in results between institutions and surgeons may simply reflect variation between patient populations, it is important to adjust for other prognostic variables[24]. In the present study adjustment was made for age, sex and tumour (Dukes) stage, which are established independent prognostic factors in rectal cancer[4,25]. In addition, adjustment was made for the use of preoperative radiotherapy.

The high rate of potentially curative resection in the Stockholm trials is likely to be explained by the eligibility criteria, which excluded emergency cases and patients with preoperative signs of distant metastases and/or irresectable tumours.

The number of rectal cancer operations performed in a hospital did not significantly influence postoperative mortality or surgical complications. There was a trend towards a reduced local recurrence rate in hospitals with more rectal cancer operations but this did not seem to influence the rate of death from rectal cancer. Patients operated on within the group of university hospitals had a significantly lower risk of local recurrence and death from rectal cancer than those from non-university hospitals. However, in some community hospitals the risk of local recurrence and death from rectal cancer were similar or lower than in university hospitals.

This study showed a relatively low case volume per surgeon. In fact, 76 per cent of the operations in the two Stockholm trials were performed by surgeons who operated on fewer than 3 included patients annually. As only patients included in the trials were studied, some surgeons may have performed proportionally more non-included rectal cancer operations during the study. However, the surgeon case volume, in terms of mean annual number of rectal cancer operations performed, did not influence patient outcome. This finding is supported by other publications, which have been unable to prove a causal link between operation volume and outcome[26–29].

However, in patients operated on by surgeons with 10 years or more experience as a specialist, local recurrence and death from rectal cancer were significantly reduced The fact that surgical skill improves with time is not surprising, but the precise technical details defining this skill are unclear. The differences in performance between surgeons can be analysed only if the operation notes include detailed information, preferably using standard forms, which was not the case in the Stockholm trials.

Meaningful analysis of between-surgeon variability requires that each surgeon does a substantial number of operations. Within the Stockholm trials, only 11 surgeons performed more than 25 rectal cancer operations. A comparison of outcome for patients operated on by these surgeons revealed a significant variation in the estimated risks of postoperative mortality and surgical complications, local recurrence and death from rectal cancer even after adjustment for other prognostic factors. However, only four individual surgeons had results that significantly differed from the others. This may be explained by the fact that the number of patients and number of events were still quite small.

As the radiotherapy technique in the two trials differed, an analysis of outcome according to the studied hospital- and surgeon-related factors was also performed for each trial separately. The results of these analyses were similar to those presented above (data not shown).

As reported previously from the Stockholm Rectal Cancer Study Group, preoperative radiotherapy reduced the overall risk of local failure by approximately 50 per cent after curative surgery for rectal cancer[7 15 16]. The local recurrence rate varied substantially between different hospitals and surgeons, some reporting low figures also in non-irradiated patients. Thus, one important question is whether institutions and surgeons with low local recurrence rates after surgery alone still should use radiotherapy as an adjunct to surgery.

In this study, the relative reduction in the local recurrence rate after preoperative radiotherapy was 20 per cent in university hospitals (with a local recurrence rate of 18 per cent in non-irradiated patients), compared with 60 per cent in non-university hospitals (with a local recurrence rate of 32 per cent in non-irradiated patients). Although the estimated proportional reduction in local failure rate differed between these two groups of hospitals, the difference was not significant. Thus, we cannot reject the hypothesis that radiotherapy reduced the rate of local recurrence similarly in hospitals with different local recurrence rates in non-irradiated patients. On the other hand, whether the same benefit of preoperative radiotherapy concerning local failure will be achieved in institutions with local recurrence rates as low as 5–10 per cent without adjuvant therapy is unknown. Although the proportional reduction of local recurrence rate with preoperative radiotherapy is probably similar in most institutions, the absolute reduction is small if local recurrence rates are already low. Thus, it must be a matter of thorough audit and clinical judgement in each institution, which policy should be used. Where local recurrence rates are less than 10 per cent after surgery alone, the benefit of preoperative radiotherapy should be balanced against the early and late adverse effects of radiotherapy[25,30].

In summary, there is significant surgeon-related variation in outcome after surgery for rectal cancer. This variability is probably related mainly to the surgical technique and not to the number of rectal cancer operations performed in the hospital or by the individual surgeon.

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Short note

Mutant plasma p53 protein levels: prognostication in colorectal carcinoma

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The 'wild type' p53 protein (p53w) is a 53-kDa cellular phosphoprotein that is responsible for control of cellular growth. It mediates a reversible arrest in the G1 phase of the cell cycle as well as apoptosis, an irreversible process culminating in cell death[1]. Because of this activity p53w is present at very low levels and under tight control in normal cells. It typically has a very short half-life of only 30 min. These normal physiological processes are necessary for the degradation of damaged cells. Loss of this tumour-suppressive function is one of the mechanisms that lead to tumorigenesis.

In contrast, the 'mutant' form of the p53 protein (p53m) accumulates in neoplastic cells and interferes with the function of the wild type in a dominant fashion; p53m alters the tetrameric binding of p53w thus changing its allosteric properties and cellular function[2]. Overexpression of cellular p53m is correlated with a higher rate of recurrence and lower survival in colorectal carcinoma[3]. Cytoplasmic accumulation of this protein is an independent prognostic indicator in colorectal adenocarcinoma[4]. Immunohistochemical techniques have been used to analyse these tissue samples in the past.

The availability of a commercial enzyme-linked immunosorbent assay (ELISA) which detects the PAb240 epitope, a frequent locus for mutation, now provides a relatively easy method of measuring plasma levels of p53m. This study aimed to determine if plasma levels of p53m correlate with the presence and stage of colorectal neoplasia compared with normal controls.

Patients and methods

Some 123 patients managed between July 1995 and September 1995 were studied. The population comprised 71 patients with a normal colonoscopic examination (controls), 12 patients with benign adenoma and 40 patients with adenocarcinoma. The mean(s.d) age was 64·9(9·5) years for patients with carcinoma, 57·8(15·8) years for those with adenoma and 48·9(13·2) years for the control group. There were 63 women and 60 men in the cohort.

Blood samples were drawn following colonoscopic examination. Plasma was separated by centrifugation and stored frozen at −70°C until the time of analysis

A commercially available ELISA (Oncogene Science, Cambridge, Massachusetts, USA) was used. The methodology has been described adequately elsewhere[5] The limit of detection using this technique was 0·05 ng/ml; a positive result was taken as ten times background or 0·5 ng/ml[5]

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Results

The results are summarized in *Table 1*. The percentages of positive tests were 20, 35 and 83 per cent for the control, carcinoma and polyp groups respectively. The sensitivity of this test as a screening tool was evaluated at 35 and 83 per cent respectively for carcinoma and polyp detection. The specificity was 80 per cent.

The mean plasma p53m protein level for control subjects was 0·37 ng/ml compared with 0·31 ng/ml for those with carcinoma and 0·84 ng/ml for patients with adenoma. Subgroup analysis for stage revealed that patients with Dukes 'D' lesions had a mean level of 0·42 ng/ml. No correlation could be found for tumour grade or size of adenoma.

Non-parametric statistical analysis using the Mann–Whitney U test showed significance only for polyps compared with normal controls ($P = 0{\cdot}0008$). The odds ratios for Dukes 'D' carcinomas and adenomas were 3·56 and 20·36 respectively, which were significant at the 95 per cent confidence intervals.

Discussion

A recent study measuring plasma p53m has shown that raised levels correlate with colorectal neoplasia[5]. The use of this modality as a screening tool, however, is disappointing. This is also borne out in the results of the present study. In fact, high background levels exist even in normal controls; the maximum value measured was 1·65 ng/ml. The possible reason for this is the interference of non-p53 cross-reacting proteins that may have led to spuriously high readings[6]. Odds ratios were only significant for Dukes 'D' carcinomas and adenomas. There are a number of possible explanations for these results: first, not all p53 mutations lead to intracellular accumulation of protein p53m[7]; second, cellular integrity needs to be breached for antigen to be expressed in plasma and this may not always occur[4]; and third, Dukes 'D' tumours have widespread metastatic spread which increases the chances

Table 1 Plasma levels of mutant p53 in various groups of patients ($n = 123$)

	No of patients	Plasma p53m (ng/ml)*	Percentage positive	Odds ratio (95% c.i.)
Controls	71	0·37(0·44)	20	1 00
Cancer	40	0·31(0 46)	35	2·19 (5·24–0·92)
Dukes 'D'	15	0·42(0 52)	47	3 56‡ (11·47–1 11)
Dukes C	10	0·22(0·35)	30	1 74 (7·49–0·40)
Dukes B	13	0·35(0·52)	31	1 81 (6·78–0·48)
Dukes A	2	n.d.	—	—
Polyps	12	0·84(0·44)	83	20·36‡ (20·36–3·99)

*Values are mean(s d.) †Percentage of patients with plasma p53m level greater than 0 5 ng/ml. p53m, Mutant p53, n.d , not detectable; c.i., confidence interval. ‡$P < 0.05$

of p53m spillover into plasma. The use of this test as an adjunct to carcinoembryonic antigen for prognostication of colorectal carcinoma needs further evaluation with larger numbers of patients.

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British Journal of Surgery 1997, 84, 665

Surgical workshop

Use of an angled knife in rectal surgery

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In recent years, in an effort to reduce the number of permanent colostomies, increasing use has been made of anterior resection in the management of rectal carcinoma. This has been achieved by lower transection of the rectum and performance of the anastomosis very low in the pelvis[1].

Many surgical modifications have been introduced to lessen the technical difficulty of such low anastomoses; these include the use of circular stapling instruments, purse-string devices, transverse stapling of the rectal stump and, occasionally, performance of the anastomosis transanally[2].

All these techniques require precise linear transection of the rectum, a manoeuvre that can be difficult in a narrow pelvis.

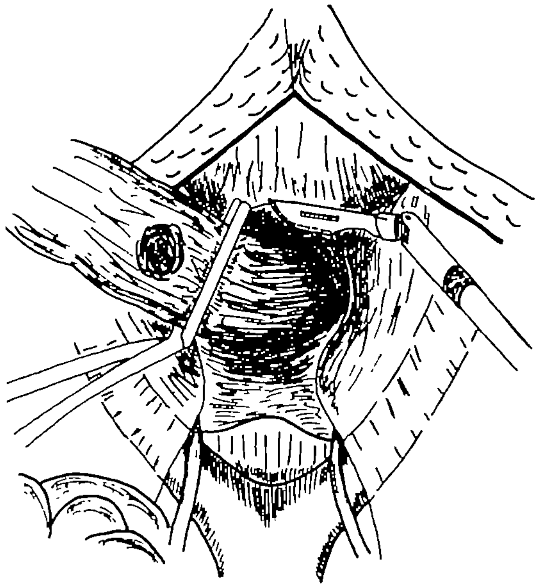

Fig. 1 Division of the rectum with the angled knife

Surgical technique

Mobilization of the colon and rectum is performed in the usual manner and the rectum is prepared for transection by application of a right-angled colonic clamp or purse-string instrument, or Roticulator (AutoSuture, Ascot, UK) if stapled closure of the stump is chosen. A Reid mitral valvotomy knife (Downs Surgical, Sheffield, UK) is used The angled knife is first set to an appropriate angle by turning the adjustable handle. The knife is directed down into the pelvis and the bowel is then transected using the edge of the clamp or Roticulator as a cutting guide (*Fig. 1*)

Discussion

The angled knife was first developed for use in cardiothoracic surgery, particularly for excision of damaged cardiac valves. However, it is equally useful in any area with limited accessibility and certainly facilitates accurate division of the rectum, with good visibility of the operative field in low anterior resection. The angled knife has the advantage for the colorectal surgeon of allowing the shaft of the instrument to be directed straight down into the pelvis, so it does not get in the way of other instruments or obscure the view of adjacent structures. It also enables the surgeon's hand to remain out of the pelvis. The blade itself is more easily visualized and more accurately controlled. Use of the angled knife is recommended in the performance of low anterior resection.

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A prospective randomized study of follow-up after radical surgery for colorectal cancer

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Background The possible benefit for patients from follow-up examinations after curative surgery for colorectal cancer is unproven. The purpose of this study was to determine whether survival is improved by frequent follow-up examinations.

Methods A total of 597 patients less than 76 years old treated with radical surgery for colorectal cancer were included in the study from 1983 to 1994. Patients were randomized to frequent follow-up (group 1) or virtually no follow-up (group 2) with examinations at 5 and 10 years.

Results Group 1 comprised 290 patients, group 2 contained 307. Recurrence was equally frequent (26 per cent), but the time of diagnosis was 9 months earlier in group 1; also, more recurrences were asymptomatic in group 1 and more patients had new surgery with curative intent ($P = 0{\cdot}02$). However, no improvement in overall survival or in cancer-related survival resulted.

Conclusion Patients subjected to intensive follow-up have recurrence diagnosed earlier, and have more operations for recurrence, but the survival results suggest that any major improvement by intensive follow-up is unlikely.

Colorectal cancer is the third most frequent cancer in developed countries and the second leading cause of cancer-related death[1] Reasons for follow-up after resection of colorectal cancer may be to detect and treat recurrent as well as new neoplasia at a curable stage. However, it is unproven whether longer survival will result from an earlier detection and treatment of recurrence and metachronous colorectal cancer[2–4], and intensive follow-up programmes, including invasive examinations, carry a small risk themselves.

The main purpose of the present randomized study was to evaluate the possible influence of follow-up upon survival.

Patients and methods

From January 1983 to June 1994, 597 patients were studied after primary radical colorectal surgery. They fulfilled the following criteria: age less than 76 years, no complicating disease making follow-up impossible, no other major cancer within the past 5 years, and permanent residency in the county of Funen.

The patients were considered to have had radical surgery when no residual neoplasia was detected by the following examinations: complete colonoscopy or incomplete colonoscopy plus double-contrast barium enema, chest radiograph (two projections), histological examination of all resection margins in surgical specimens, biopsy of lesions (including lymph nodes) which could be neoplastic by inspection and/or palpation, and inspection and palpation of the liver during surgery[4]. Methods of histopathology have been reported previously[5,6] All patients were also instructed to visit their general practitioner if they developed abdominal pain or changing bowel habits lasting more than 2 weeks after the immediate postoperative period.

After surgery, the patients were allocated to one of two follow-up programmes (groups 1 and 2) by random numbers, stratified within the three Dukes stages[7] and according to three different tumour locations (rectum, sigmoid and other parts of the colon). Group 1 had follow-up examinations at 6, 12, 18, 24, 30, 36, 48, 60, 120, 150 and 180 months after radical surgery, while group 2 had examinations at 60, 120 and 180 months

The examinations included medical history, clinical examination, digital rectal examination, gynaecological examination, Haemoccult-II test (SmithKline Diagnostics, San Jose, California, USA), colonoscopy, chest radiograph, haemoglobin level, erythrocyte sedimentation rate and liver enzymes. Whenever recurrence was suspected, more detailed examinations were performed to detect possible treatable recurrence.

Local recurrence was defined as tumour growth in the region of the primary radical operation, including the surgical wound, and demonstrated clinically or by imaging techniques, but not necessarily verified by biopsy. Colorectal cancer was considered to be metachronous when diagnosed at least 12 months after primary cancer

Statistical analysis was based on Kaplan–Meier survival functions, differences in survival were estimated by the log rank test Fisher's exact and χ^2 tests were used for unpaired groups, the Mantel–Haenszel test was used for stratified analysis Statistical significance was set at $P < 0{\cdot}05$ The study was designed to demonstrate a possible reduction in mortality rate (uncorrected) of 20 per cent (power 0·80, $P < 0{\cdot}05$)

Results

The distribution of sex ($P = 0{\cdot}13$) and age ($P = 0{\cdot}47$) in groups 1 and 2 is presented in *Table 1*.

By June 1994 recurrence (local and/or distant spread) was detected in 76 patients in group 1 and 80 in group 2. No difference in survival rate before detection of recurrence was found (*Fig. 1*). However, in patients who had recurrence, the cancer-free time was significantly shorter in group 1 (18 months) compared to group 2 (27 months) (*Fig 2*).

Follow-up for more than 5 years was possible in 310 patients (159 in group 1 and 151 in group 2). Of the 98 recurrences, 49 in each group, 84 and 59 per cent respectively were diagnosed in the first 3 years. These figures rose to 94 and 88 per cent respectively within the first 5 years of follow-up.

The distribution of asymptomatic and symptomatic recurrence (local and distant) between the two groups in relation to new curative surgery is shown in *Table 2*. In group 1, more recurrences were asymptomatic ($P = 0{\cdot}02$) and a larger proportion of the recurrences had new

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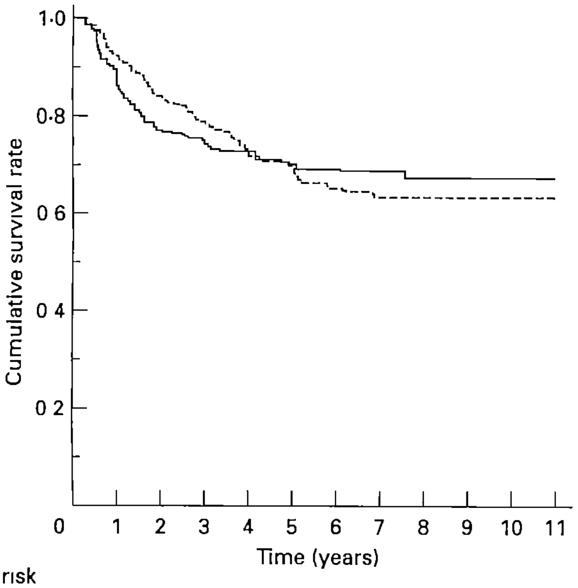
Table 1 Distribution of sex, age, location of primary cancer and Dukes stage

	Group 1	Group 2
Sex		
Men	168 (58)	158 (51)
Women	122 (42)	149 (49)
Age distribution		
<51	20 (7)	26 (8)
51–60	68 (24)	59 (19)
61–70	137 (47)	159 (52)
71–75	65 (22)	63 (21)
Location		
Rectum	134 (46)	149 (49)
Sigmoid	64 (22)	66 (21)
Remaining colon	92 (32)	92 (30)
Dukes stage		
A	68 (23)	70 (23)
B	148 (51)	145 (47)
C	74 (26)	92 (30)

Values in parentheses are percentages

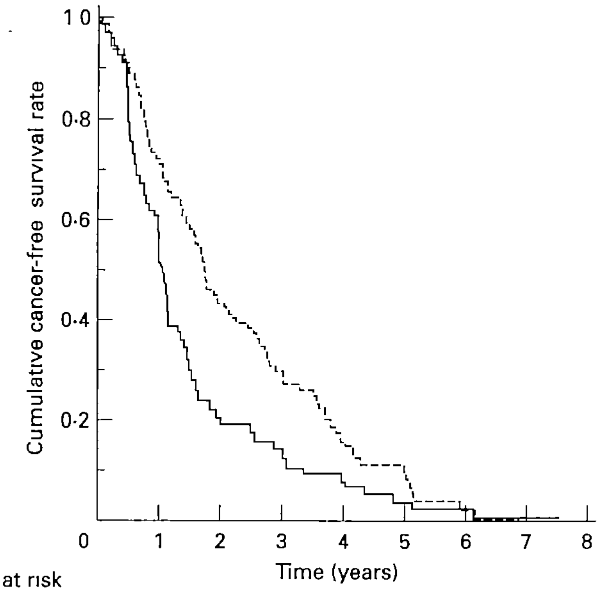


No. at risk						
Group 1	290	176	122	81	39	13
Group 2	307	199	132	73	39	5

Fig. 1 Cumulative cancer-free survival rate in groups 1 (——) and 2 (---). $P=0{\cdot}78$ (log rank test)

surgery with curative intent ($P<0{\cdot}01$). However, when controlled for the follow-up programme no association was found between symptoms at recurrence and curative therapy (Mantel–Haenszel test, $P=0{\cdot}94$), whereas an association still existed between group allocation and curative therapy when controlled for the occurrence of symptoms (Mantel–Haenszel test, $P=0{\cdot}02$).

Local recurrence as first recurrence (with or without distant spread) was diagnosed in 17 per cent (49 of 290) of group 1 and 14 per cent (42 of 307) of group 2 (*Table 3*). Local recurrence as first recurrence of rectal cancer was diagnosed in 22 per cent (30 of 134) of group 1 patients and in 19 per cent (28 of 149) of group 2. At the time of detection, 31 per cent (15 of 49) of group 1 and 2 per cent (one of 42) of group 2 patients had no symptoms.



No. at risk					
Group 1	76	16	6	2	1
Group 2	80	36	12	2	0

Fig. 2 Cumulative cancer-free survival rate in patients with recurrence in groups 1 (——) and 2 (---) $P<0{\cdot}01$ (log rank test)

Table 2 Symptoms at first recurrence (local and distant) in the two groups related to new curative therapy

	Asymptomatic	Symptomatic
Group 1		
Intended curative therapy	9	6
Palliative or no therapy	29	32
Group 2		
Intended curative therapy	0	5
Palliative or no therapy	11	54

Table 3 Number of patients with recurrence of cancer and metachronous cancer in relation to site and symptoms in groups 1 and 2

	Group 1	Group 2
Local recurrence		
Without symptoms	13	1
With symptoms	29	31
Local recurrence and distant spread		
Without symptoms	2	0
With symptoms	5	10
Distant spread		
Without symptoms	23	10
With symptoms	4	28
Metachronous cancer		
Without symptoms	6	2
With symptoms	1	1

New surgery with curative intent was carried out in 22 per cent (11 of 49) of group 1 and 7 per cent (three of 42) of group 2 patients with recurrence ($P=0{\cdot}15$); five of 11 in group 1 and one of three patients in group 2 were without disease in June 1994 (time of observation 24, 8, 63, 95 and 12 months in group 1, and 6 months in group 2). The rates of patients with cured local recurrence in groups 1 and 2 were 1·7 and 0·3 per cent respectively ($P = 0{\cdot}20$).

Distant spread as first recurrence (with or without local recurrence) was diagnosed in 12 per cent (34 of 290) of group 1 and 16 per cent (48 of 307) of group 2 patients. No symptoms were present in 74 per cent (25 of 34) of group 1 and 21 per cent (10 of 48) of group 2 patients (*Table 3*). New surgery with curative intent was performed in 12 per cent (four of 34) of group 1 patients and 4 per cent (two of 48) of group 2 patients with distant spread ($P = 0{\cdot}42$). Among the remaining 76 patients (30 in group 1 and 46 in group 2) no more than two had resectable distant metastases, but surgery could not be offered because of complicating disease and refusal by the patient of further treatment. In June 1994 two of four patients in group 1 were still without disease after 2 and 4 years of observation, while the two patients in group 2 both had a new recurrence. The rates of cured distant recurrence in groups 1 and 2 were 0·6 and 0 per cent respectively ($P = 0{\cdot}47$).

Metachronous cancer was detected in seven patients in group 1 and three in group 2 (*Table 3*). New curative surgery (using the same criteria as for primary curative surgery) was performed in six in group 1 and two in group 2, and three and one patients in groups 1 and 2 respectively remained free of disease.

Overall, nine of 81 patients with diagnosed recurrence in group 1 and two of 83 in group 2 remain without any further recurrence at the present time after having had surgery with curative intent or new curative surgery for metachronous cancer.

In all, 88 of 290 patients in group 1 and 100 of 307 in group 2 have died. There was no significant difference between survival in the two groups (*Fig. 3*). Survival rate(s.e.) at 5 years was 0·70(0·03) in group 1 and 0·68 (0·03) in group 2. In all, 61 patients in group 1 and 65 in group 2 have died of colorectal cancer without any difference in survival between the two groups (*Fig. 4*).

Discussion

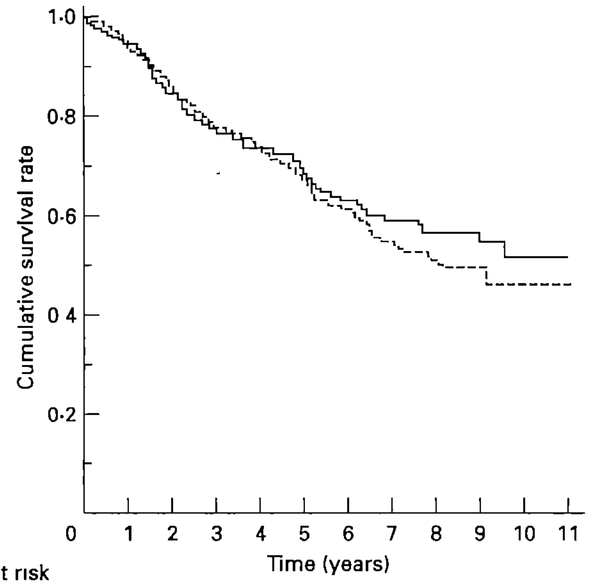
The proportion of men tended to be higher in group 1, but this possible bias towards shorter survival in group 1 is counterbalanced by the stratification according to Dukes stage and location of tumour.

In the present study the frequency of recurrent cancer was similar in the two groups, but recurrence in group 1 was diagnosed earlier (*Fig. 2*). It should be emphasized that the final recurrence rate will not be available before 1997, when all patients will have been followed up for at least 3 years.

The mean difference in time until diagnosis of recurrence between groups 1 and 2 was 9 months, which is longer than the lead time of 4–6 months obtained with planned frequent measurements of carcinoembryonic antigen (CEA) every second or third month[8–10]. The present longer lead time may to some degree be explained by the use of several diagnostic screening procedures, but delay from first symptom to examination for possible recurrence may have been longer in group 2.

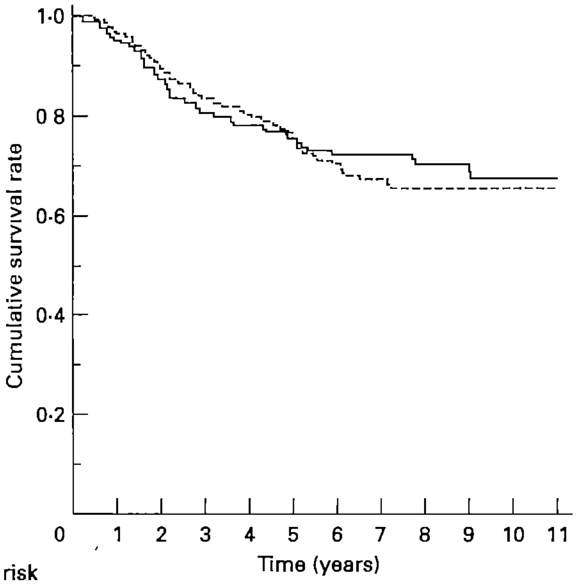
The interval of 6 months during the first 3 years was chosen to reduce the anxiety of the patients, but shorter intervals of a few weeks might have increased the chance of curative surgery for recurrence[11]. Reduction of the interval from 6 to 3 months would probably not have increased this chance, considering that the lead time, using CEA monitoring every 2–3 months, was no more than 4–6 months in the literature compared to the present 9 months[8–10].

In group 1, more recurrences were removed by new curative surgery; but no association was found between asymptomatic recurrence and new surgery with curative intent (*Table 2*; Mantel–Haenszel test, $P = 0{\cdot}94$). This is in contrast to previous large retrospective studies using CEA[12,13], but the present randomized study confirms that



No. at risk						
Group 1	290	203	133	85	43	13
Group 2	307	212	144	78	40	5

Fig. 3 Cumulative survival rate in groups 1 (——) and 2 (– – –). $P = 0{\cdot}48$ (log rank test)



No. at risk						
Group 1	290	203	133	85	43	13
Group 2	307	212	144	78	40	5

Fig. 4 Cumulative cancer-related survival rate in groups 1 (——) and 2 (– – –). $P = 0{\cdot}90$ (log rank test). (Patients who died from other causes than colorectal cancer are censored)

an early diagnosis of recurrence increases the chances of new curative surgery.

The proportion of patients cured from local or distant recurrence or from metachronous cancer was higher in the group with intensive follow-up, but the difference is small, and the time of observation after curative surgery for metachronous cancer is very short in some patients[2,14].

During the period 1983–1994 ten metachronous cancers were found. The distribution in groups 1 and 2 could be due to random variation ($P = 0{\cdot}31$), and a longer period of follow-up will be necessary to demonstrate the possible influence of frequent colonoscopy with polypectomy in group 1 on the incidence of metachronous cancer.

It has been suggested that the endpoints of follow-up should be mortality and survival rates instead of treatable recurrence[15]. In the present study the overall survival and cancer-related survival rates in groups 1 and 2 are similar (*Figs 3* and *4*).

A meta-analysis of retrospective figures has suggested that monitoring of CEA is essential for improvement in survival rate[16], but others have not been able to support this[17,18], and results from the only major randomized study suggested no reduction in mortality rate (Northover, personal communication, quoted in reference 19). CEA was not used in the present follow-up examinations.

It could be argued that more resectable distant metastases would have been found if more sensitive markers for distant spread had been used, such as CT scan and ultrasonography of the liver, and chest tomography. The present protocol is now being followed by a prospective evaluation of the yield of resectable liver metastases by performing intraoperative ultrasonography and repeating the ultrasonography every 6 months during the first 3 years after surgery.

In conclusion, patients allocated to a frequent follow-up programme had earlier diagnosis of recurrence and more frequent new surgery with curative intent. Unfortunately, the present study is too small to demonstrate a reduction in mortality rate of less than 20 per cent by intensive follow-up, but the possibility of new curative surgery for recurrence in 2·3 per cent of all patients in group 1 compared to 0·3 per cent in group 2 does not seem to justify the present type of intensive follow-up. Favouring the possibility of curing more metachronous cancer in group 1 might increase the percentages to 3·1 and 0·6 respectively. A larger study would have been desirable, but only a multicentre trial would have overcome the drawback of the very long period of intake. A separate analysis is planned, comparing sensitivity and specificity of different diagnostic methods for detection of recurrence within the present randomized study.

Acknowledgements

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Short note

Intradermal methylene blue injection for the treatment of intractable idiopathic pruritus ani

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Symptoms of idiopathic pruritus ani may remain severe despite treatment. The outcome from intradermal methylene blue injection is reported.

Methods

The patient is counselled that short-term tattooing of the skin and the appearance of blue urine occurs after the procedure. Under general anaesthesia, intravenous cefuroxime 750 mg and metronidazole 500 mg is given, the patient is placed in the lithotomy position, and the perianal skin is prepared with povidone–iodine solution. Ten millilitres methylene blue 1 per cent mixed with 7·5 ml Marcain (Astra, Kings Langley, UK) 0·25 per cent with adrenaline 1:200000, 7·5 ml Marcain 0·5 per cent and 5 ml sodium chloride 0·9 per cent solution is delivered via a 22-G spinal needle. The methylene blue is infiltrated intradermally along skin furrows, incorporating any areas of excoriated tissue (*Fig. 1*).

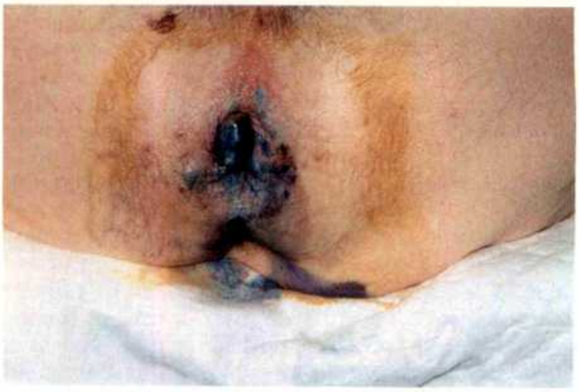

Fig. 1 Perianal appearance after intradermal injection of methylene blue in a patient with intractable pruritus ani

Results

Six consecutive patients (5 men) of median age 56 (range 25–76) years with severe, intractable pruritus ani and marked perianal excoriation who presented to one surgeon (P.W.R.L.) were treated. No patient had faecal incontinence or previous anorectal surgery. Each patient was investigated by stool culture, skin scrapings for fungal infection and proctoscopy combined with a barium enema to exclude other pathology. No co-existing pathology, including significant haemorrhoids, was identified. All patients failed to respond to traditional treatment, including advice about perianal hygiene, and avoidance of topical agents.

After operation one patient developed urinary retention which required temporary catheterization, another had a superficial abscess, and one suffered transient incontinence. In five cases, there was a substantial reduction in symptoms after treatment, with marked regression of associated skin changes and only occasional minor symptoms of pruritus. All patients reported a numb sensation in the perianal area following the procedure which persisted at follow-up. While this was not compared objectively before and after operation, there was a subjective reduction in light touch and pin-prick sensation in the perianal region. No patient reported the numbness to be troublesome.

The median duration of follow-up was 3 (2–5) years. Three patients had a second injection of methylene blue for recurrent symptoms at 1, 3 and 5 years. All had initial numbness after the first injection.

Discussion

Previous attempts to treat intractable pruritus ani include perianal injection of anaesthetic agents[1], surgical disruption of the sensory nerve supply to the perianal area[2] and cryotherapy[3]. Sepsis and skin necrosis have been the primary drawbacks of these procedures. Intradermal methylene blue injection has been shown by electron microscopy to destroy dermal nerve endings[4]. When used previously for pruritus ani, it provided relief of symptoms but was associated with skin necrosis in 25 per cent of patients[4].

The technique described in this paper used a smaller total volume of methylene blue and local anaesthetic than was used previously. There was no skin necrosis in this series. The long-term relief attained was variable; three patients in the series required a second injection. The reduction in the extent of excoriation and relief of symptoms was substantial in a group who had previously failed to respond to conventional therapy.

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Short note

Recognition of a pathological appendix during laparoscopy: a prospective study of 81 cases

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Between 20 and 30 per cent of appendices removed are normal; no investigation reliably improves the accuracy of diagnosis[1]. Laparoscopy allows other pathologies to be diagnosed and an assessment of the appendix. This study tests the accuracy of ten surgeons' visual assessment.

Patients and methods

Laparoscopy for acute right iliac fossa pain was performed in 81 patients (48 women and 33 men) of mean age 27 (range 17–73) years during a 6-month period in 1995. Four photographs of each appendix were taken before dissection was started (*Fig. 1*). The photographs were coded and the appendices later classified as normal or inflamed by ten surgeons (five junior and five senior). The histopathologist (M.Z.) classified the appendices into three groups: acute appendicitis, mucosal inflammation alone, or normal.

Results

Of the 81 patients, 16 had other pathologies to explain their symptoms; the appendix was left and they were excluded from the analysis. A laparoscopic appendicectomy was, therefore, performed in 65 patients; none was converted to open operation. The histopathologist reported 38 appendices as having acute inflammation, seven mucosal inflammation alone and 20 as normal. If the seven cases of mucosal inflammation are considered as pathological, the overall sensitivity of the visual evaluation was 92 per cent and the specificity 85 per cent. If they are considered as non-pathological, the sensitivity rises to 100 per cent and specificity falls to 78 per cent. The concordance of visual evaluation and histopathology was independent of the experience of the surgeon ($P = 0{\cdot}71$, Student t test). The surgeon who classified the highest number of appendices as inflamed would have removed seven of 20 normal and five of seven mildly inflamed organs. The surgeon who classified the lowest number as inflamed would have removed only two of 20 normal and three of seven mildly inflamed appendices (leaving four to evolve). All surgeons accurately recognized acute appendicitis involving the serosa.

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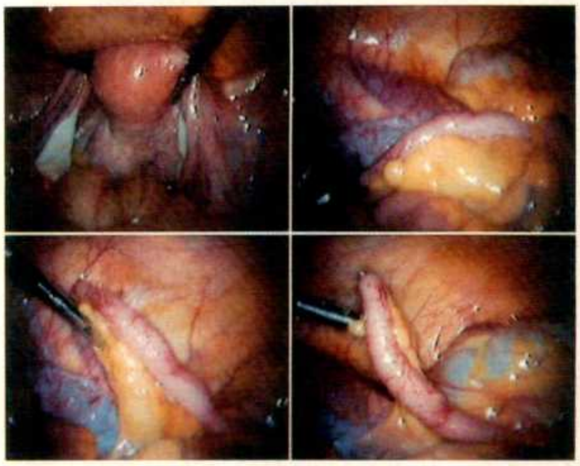

Fig. 1 Typical example of photographs of the appendix

Discussion

Laparoscopic appendicectomy has very few advantages over the open approach[2] and has not been widely adopted[3]. Laparoscopy can, however, make an accurate diagnosis in right iliac fossa pain[4]. Despite having only photographs, the visual assessments by all surgeons were extremely accurate.

No-one missed acute appendicitis that involved the serosa. Half of the cases of mucosal inflammation only were judged normal. Does the potential morbidity of the appendicectomy in these cases outweigh the danger of leaving in place a mildly inflamed appendix? The policy now being studied in this unit is to trust the visual assessment, and, if the organ appears normal, it is left in place. Three doses of antibiotics are given as prophylaxis to all patients and since antibiotics have been proven to be as effective as surgery for acute appendicitis[5], it may be that this is sufficient to treat effectively the missed cases of early inflammation. If this policy had been adopted during the present study, three minimally inflamed (5 per cent of the total group) and 16 normal (24·6 per cent) appendices would have been left in place.

In conclusion, visual inspection during laparoscopy is extremely sensitive and specific for acute appendicitis. In approximately one in 20 cases, early appendicitis may be inadvertently judged as normal.

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Management of ileosigmoid knotting

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Background Ileosigmoid knotting is a rare cause of intestinal obstruction.

Methods The clinical records of 16 patients treated for ileosigmoid knotting were evaluated retrospectively.

Results There were 11 men and five women. The mean age was 45 years. The mean duration of symptoms was 4·4 days. Plain abdominal radiographs showed multiple air–fluid levels in the colon and/or small bowel. At operation, ileum and/or sigmoid colon necrosis was observed in 13 patients, both ileum and total colon necrosis in two, while there was no necrosis in one patient. Resection of necrotic bowel was necessary in 15 patients. Intestinal continuity was restored by primary anastomosis in 12; three required a stoma. The patient without necrosis was treated by detorsion and mesosigmoplasty. Three of 16 (19 per cent) patients died; septic shock was the major cause of death.

Conclusion Aggressive preoperative resuscitation, appropriate antibiotic therapy, effective surgery and postoperative metabolic support help minimize morbidity and mortality rates.

Ileosigmoid knotting, also known as compound or double volvulus, is a rare cause of intestinal obstruction[1–5]. Three factors are responsible for the ileosigmoid knot: first, a long small bowel mesentery and freely mobile small bowel; second, a long sigmoid colon on a narrow pedicle, and finally the ingestion of a high-bulk diet in the presence of an empty small bowel. When a semiliquid bulky meal progresses into the proximal jejunum, it increases the motility of the intestine, and heavier segments of proximal jejunum fall into the left lower quadrant. The empty loops of ileum and distal jejunum twist in a clockwise rotation around the base of a narrow sigmoid colon. Further peristalsis forms an ileosigmoid knot with two closed loop obstructions, one in the small bowel and one in the sigmoid colon[1–7]. Evidence for this mechanism is suggested by studies carried out on the Bagandans in Uganda, who eat once a day, and Muhammadans who eat a single daily meal during the Ramadan fast[3,4,6].

Patients and methods

The records of 16 patients treated for ileosigmoid knotting at Dicle University Hospital between 1985 and 1995 were reviewed retrospectively. The historical, clinical and radiological findings were studied. All patients needed active resuscitation with rapid fluid–electrolyte infusion and nasogastric decompression. All patients received antibiotic therapy for at least 7 days. Following resuscitation, midline laparotomy was carried out under general anaesthesia. Infarcted bowel was excised and intestinal continuity was restored by primary anastomosis if possible. After operation total parenteral nutrition was continued until the return of bowel sounds.

Results

The mean age of the patients was 45 (range 20–90) years. Eleven were men and five women, one of whom was 6 months pregnant. The mean duration of symptoms before presentation was 4·4 (range 1–6) days (*Table 1*). A history of chronic constipation was not a feature. Nine patients were admitted as a surgical emergency with septic shock. Radiological findings usually consisted of dilated large and small bowel with multiple air–fluid levels (*Fig. 1*). Laparotomy findings and surgical procedures are documented in *Table 2*.

Three of 16 patients died; septic shock was the major cause of death. One 90-year-old patient who had total colon and ileal necrosis died from multiple organ failure on the fourth postoperative day. One patient who had a gangrenous ileum and sigmoid colon died from septicaemia in the early postoperative period. A patient with gangrenous ileum and viable sigmoid colon died from septic shock caused by enterocutaneous fistula on the tenth postoperative day. All patients who died had been admitted with septic shock.

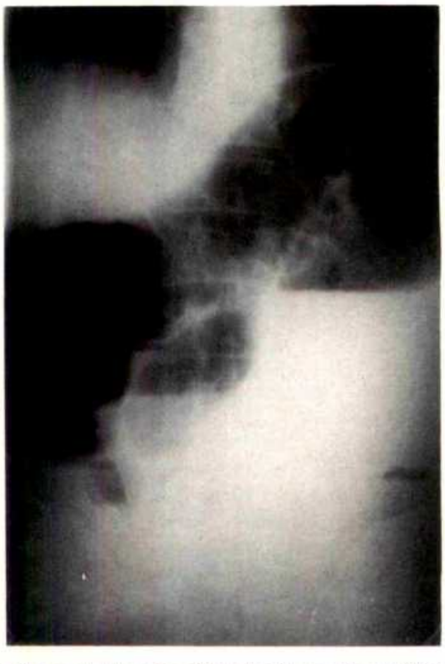

Fig. 1 Radiograph showing dilated colon and small bowel with multiple air–fluid levels in a patient in the erect position

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Table 1 Symptoms and signs of ileosigmoid knotting

Symptoms and signs	No. of patients
Abdominal pain and tenderness	16 (100)
Abdominal distension	15 (94)
Nausea and vomiting	14 (87)
Rebound tenderness	11 (69)
Constipation	9 (56)

Values in parentheses are percentages

Table 2 Surgical procedures and deaths

Laparotomy finding	Surgical procedure	No. of patients	No. of deaths
Gangrenous ileum and viable sigmoid colon	Ileal resection + primary anastomosis + colonic detorsion	4	0
	Ileal resection + primary anastomosis + mesosigmoplasty	2	1
Gangrenous ileum and sigmoid colon	Ileal and sigmoid resection + primary anastomosis	3	0
	Ileal and sigmoid resection + primary anastomosis + end ileostomy	1	1
Gangrenous sigmoid colon and viable ileum	Sigmoid resection + primary anastomosis	3	0
Gangrenous total colon and ileum	Total colectomy + ileal resection + end ileostomy	2	1
Viable ileum and sigmoid colon	Detorsion + mesosigmoplasty	1	0

One patient who had massive small bowel resection developed short bowel syndrome. Two months later 8 cm of remaining small bowel was constructed into a nipple valve to delay intestinal function[8]. This patient made a good recovery.

Discussion

Ileosigmoid knotting can rapidly progress to gangrene of the ileum as well as the sigmoid colon[2,7]. Generalized peritonitis, sepsis and dehydration are the principal complications. Initial management involves resuscitation in the recovery room; fluid–electrolyte and acid–base balances are corrected with the help of central venous pressure monitoring. After haemodynamic stabilization, laparotomy should not be delayed[3,4,7].

Appropriate antibiotic therapy should be commenced early and continued after operation[4]. The usual antibiotic combination includes cephalosporin, aminoglycoside and/or metronidazole.

The anatomical and pathological changes dictate the operative procedure. If both loops are viable, the knot may be undone by sigmoid enterotomy and traction of the sigmoid loop. This procedure may also be selected when the sigmoid colon alone is viable. When the ileum and sigmoid colon are gangrenous, difficulty untying the knot can cause rupture and spillage of toxic bowel contents or release of bacterial toxins into the circulation. Therefore, intestinal clamps should be applied before dissection or resection of the knot, followed by resection of both loops[1-7].

Primary anastomosis of the small bowel is preferable, but if the terminal ileum is gangrenous to within 10 cm of the ileocaecal valve, an end-to-end anastomosis should not be attempted. The distal stump should be closed and end-to-side ileocaecostomy performed[2,3,7].

Resection of the sigmoid colon is often advised in all instances even when viable. Recurrent volvulus or repeat knotting due to redundancy of the loop may cause gangrene after operation[1,3,6,7]. Until 10 years ago, all publications advocated either a Hartmann's operation or a covering colostomy because of the risk of a faecal leak from the colonic anastomosis[3,4]. However, recent data suggest that primary colonic anastomosis may be undertaken safely when the history is short and the remaining bowel clean, well vascularized and undistended[2,7]. Intraoperative colonic irrigation followed by resection and primary anastomosis is another alternative[9]. In the present study, this technique was used successfully in the last five patients with a gangrenous sigmoid colon. In three patients without sigmoid gangrene, mesosigmoplasty[10] was performed to prevent recurrent ileosigmoid knotting. No recurrent attacks have been observed in a mean follow-up of 15 months.

Because of septicaemia in patients with ileosigmoid knotting, there is a negative nitrogen balance. Therefore, all patients should be given adequate nutritional and metabolic support after operation[4].

The mortality rate following ileosigmoid knotting is about 15–73 per cent, in spite of early presentation and the absence of gangrene[3,6,7]. Although the mean duration of symptoms before presentation was more than 4 days, the mortality rate was 19 per cent (three of 16 patients), and septic shock was the major cause of the death in this series.

Rapid fluid resuscitation, preoperative broad-spectrum antibiotic therapy, prompt laparotomy, effective surgery including resection of gangrenous intestine and/or mesosigmoplasty if the sigmoid colon is viable, optimize survival in this condition.

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Case report

Management of benign rectal stricture by implantation of a self-expanding prosthesis

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The self-expanding Wallstent prosthesis (Schneider, Bülach, Switzerland) is a safe and reliable method for relieving malignant obstruction of the left colon and rectum, and can simplify management with regard to both palliation and cure[1,2].

The results of this method are reported for a patient with postoperative benign rectal stricture.

Case report

A 62-year-old woman underwent rectal resection with colorectal anastomosis in 1991 for a large adenoma. A postoperative anastomotic leak was managed conservatively. The patient was discharged on the 20th postoperative day.

Some 2 years later she developed low bowel obstruction and a colostomy was performed. Barium enema showed a 9-mm wide stricture at the site of the anastomosis (*Fig. 1a*). Recurrence of tumour was ruled out by endoscopic biopsy.

After two unsuccessful attempts at balloon dilatation, a Wallstent was implanted by the procedure described[3] in 1994. Adequate dilatation was achieved and the colostomy was closed. Normal bowel transit returned (*Fig. 1b*).

One year later, endoscopy and biopsy showed complete epithelization of the prosthesis with no pathological mucosal changes.

Discussion

Implantation of an expanding metal stent was undertaken to relieve a benign stricture of the rectum, thus avoiding a surgical procedure. The procedure offers a good alternative to the standard treatment of benign stricture when balloon dilatation fails.

In this case permanent and effective relief of obstruction was achieved, demonstrating for the first time, to the authors' knowledge, the good long-term tolerance of an intrarectal Wallstent.

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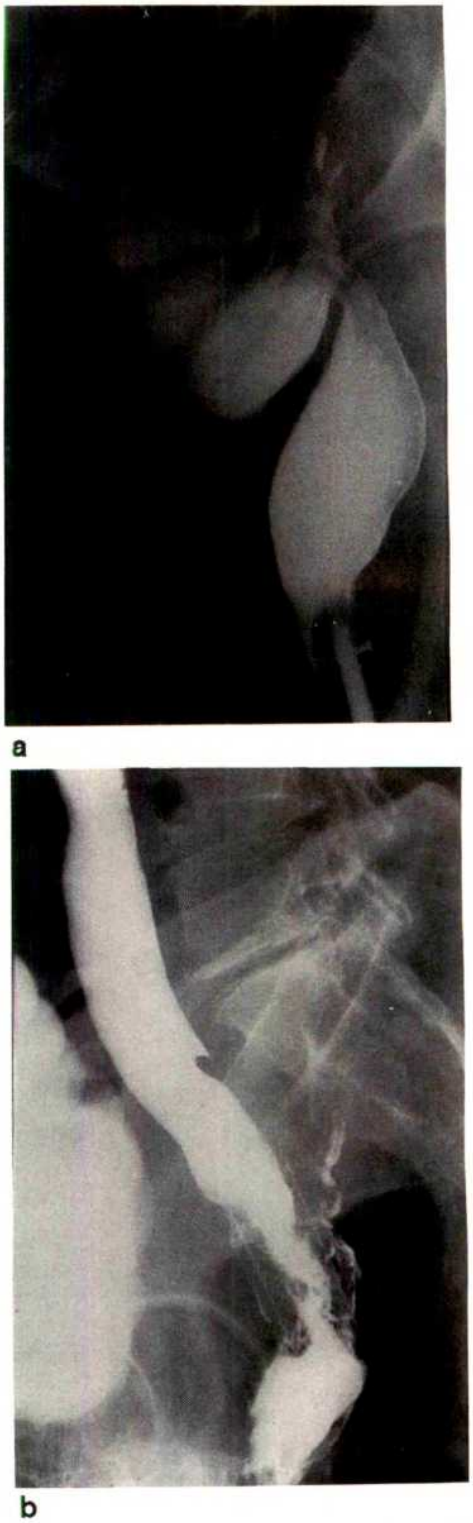

Fig. 1 a Barium enema showing a 9-mm wide stricture at the site of rectal anastomosis. **b** Opened stricture after expansion of the Wallstent prosthesis

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Skin appendage involvement in anal intraepithelial neoplasia

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Background High-grade anal intraepithelial neoplasia (AIN III) may be premalignant. Surgical excision of large areas of anal epithelium carries significant morbidity. Ablation treatments may carry less morbidity; however, the depth of ablation is uncertain and failure to ablate dysplasia in hair shafts and other skin appendages may lead to early recurrence.

Methods This study assesses morphometric aspects of skin appendages in perianal skin and anal canal mucosa in tissues from 30 patients with AIN III. Both normal and dysplastic epithelium was assessed in each patient. The depth to which AIN III involved skin appendages was measured using computerized image analysis.

Results Both the perianal epidermis and anal canal mucosa affected by AIN III were significantly thicker than normal. Nineteen of 30 patients with AIN III had skin appendage involvement. Some 57 per cent of hair follicles (79 of 138), 16 per cent of sebaceous glands (11 of 69) and 25 per cent of sweat glands (24 of 96) observed beneath an abnormal epithelium had evidence of AIN. The median depth of AIN involvement of the hair follicle was 1·14 (range 0·44–1·67) mm, sebaceous glands 1·44 (range 0·96–1·90) mm, and sweat glands 0·94 (range 0·50–2·20) mm. These figures do not take into account tissue shrinkage due to histological processing.

Conclusion AIN III involvement of epithelial appendages is a significant problem. For disease eradication, tissue destruction or removal to a depth of at least 2·2 mm below the adjacent basement membrane is required. Surgical excision of high-grade AIN remains the treatment of choice.

Anal intraepithelial neoplasia (AIN) has been described recently. Its natural history and malignant potential are uncertain[1]. The aetiology of AIN mirrors that of gynaecological intraepithelial neoplasia (cervical, vulval and vaginal), with a common factor being oncogenic human papillomavirus infection (type 16)[2–4]. Low-grade disease (AIN I/II) is thought to have little malignant potential and many of the lesions appear to regress. There is evidence that high-grade disease (AIN III) may have malignant potential and some clinicians advocate surgical excision[5].

Treatment of high-grade anal disease by surgical excision has been described[6,7]. Excision allows a full histological assessment and reduces the risk of missing microinvasive carcinoma. Excision of large areas of AIN in the anal canal (greater than 50 per cent of the circumference) requires at least a two-stage procedure including the formation of a loop colostomy and split skin grafting to the anal canal[5]. Such procedures carry appreciable morbidity.

Ablation of AIN by carbon dioxide laser vaporization or cryosurgery is attractive as a potentially less traumatic treatment option than excision. Successful ablation depends upon complete eradication of dysplasia. In the gynaecological intraepithelial neoplasias (cervical and vulval) dysplasia may penetrate into the shafts of skin appendages: hair follicles, sebaceous glands and both apocrine and eccrine sweat glands[8–11]. Recurrence following ablational treatment may be attributed partly to untreated disease in glands and hair follicles[12].

The aim of this study was to determine whether skin appendages are involved in AIN and to assess the depth of any involvement. The thickness of the normal and high-grade dysplastic epithelium in perianal skin, anal canal and anal transition zone mucosa was also measured, as well as the depth of normal skin appendages.

Patients and methods

The study included 30 patients with high-grade AIN. Nine had undergone resection of the perianal skin and anal canal; the remainder had a combination of punch biopsy and local excision. The median age of the patients was 37 (range 20–81) years. All histological specimens were fixed in formalin and embedded in paraffin. Sections were cut 4–6 μm thick and stained with haematoxylin and eosin. A total of 300 slides was examined (taken from 128 separate tissue blocks, median 3 (range 1–18) tissue blocks per patient). Only sections featuring vertically cut surfaces were examined; some tissue blocks were reorientated to provide vertical sections of epithelium.

AIN is characterized by a loss of epithelial cellular maturation with associated nuclear hyperchromasia, polymorphism, cellular crowding and abnormal mitoses within the anal epithelium. In high-grade AIN (AIN III) there are cellular and nuclear abnormalities occupying more than two-thirds of the epithelium, but without a breach of the basement membrane.

All measurements were performed using a light microscope connected to a calibrated computerized image analysis system (Seescan, Cambridge, UK). The thickness of normal and diseased epithelium was measured from the keratin–spinosum junction to the base of a perpendicularly cut rete peg. Normal epithelium was characterized by normal cellular configuration and differentiation. Only epithelium within at least three perpendicularly cut epithelial pegs was measured and the mean of these measurements was taken.

The depth of the skin appendages was assessed. Skin appendages consisted of hair follicles, and sebaceous, sweat and

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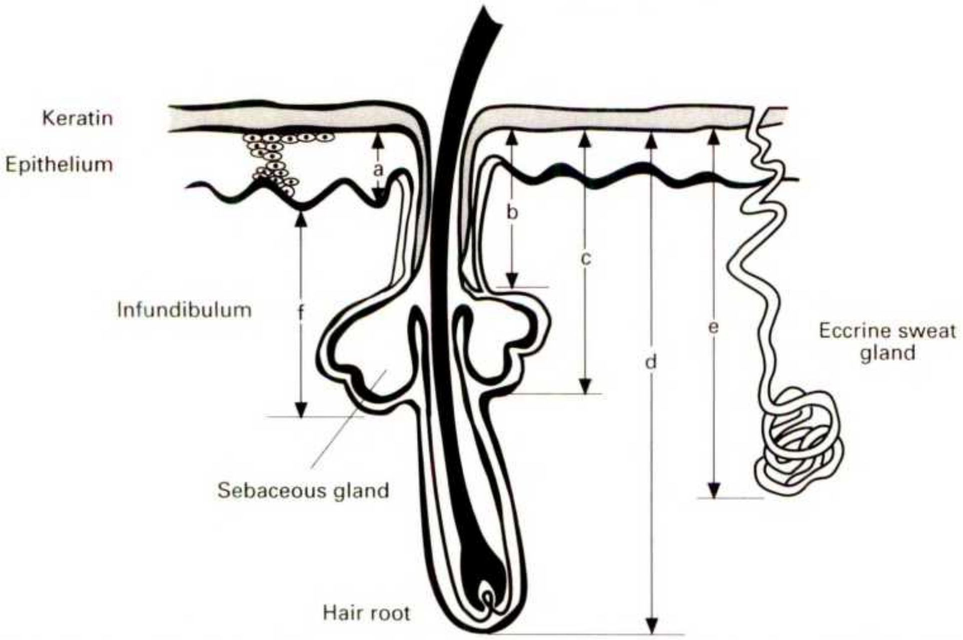

Fig. 1 Diagrammatic illustration of the range of measurements taken: epithelial thickness (a), depth of hair infundibulum (b), sebaceous gland (c), hair follicle (d) and sweat gland (e) measured from the keratin–spinosum layer; and depth of sebaceous gland (f) measured from the base of the adjacent rete peg

apocrine glands. The infundibulum is the superficial portion of the hair follicle above the insertion of the sebaceous gland. The appendage depth was measured from either the keratin–spinosum junction or the base of the adjacent rete peg to the deepest portion of the appendage (*Fig. 1*). The depth of disease penetration into the appendages was measured from the same origins. Hair follicles may run transversely beneath a perpendicularly cut epithelium and may act as a reservoir of disease. Disease-affected hair follicles in this situation were also measured.

The prevalence of disease penetration into skin appendages was also examined. The total number of skin appendages beneath diseased epithelium was counted and the proportion involved was ascertained. The depth of the dermal–subcutaneous junction was also measured in normal and diseased tissue.

The thickness of the keratin layer was assessed but a number of problems prevented reliable results being reproduced. The keratin layer undergoes both fragmentation and separation from the epithelium during fixation and so measurements were unreliable.

All measurements were made independently by two observers (P.P.S. and O.A.O.) and all cases of appendage involvement with disease were confirmed by an experienced histopathologist (J.H.F.S.). To reduce intraobserver error, all measurements were repeated at a later date and only concordant results taken.

The number of samples analysed for individual patients varied. To avoid bias from an individual with multiple tissue blocks for analysis, only the mean results for epithelial thickness, appendage depth and disease penetration for each individual were taken.

The Wilcoxon rank sum test for unpaired specimens was used to compare normal and diseased epithelium.

Results

The results indicate that AIN involves skin appendages; 19 of 30 patients with high-grade AIN had subepithelial disease involving either hair follicles (*Fig. 2*) or sweat glands. The prevalence, in this series, of disease penetration into individual hair follicles and sweat glands was 57 and 25 per cent respectively (*Table 1*).

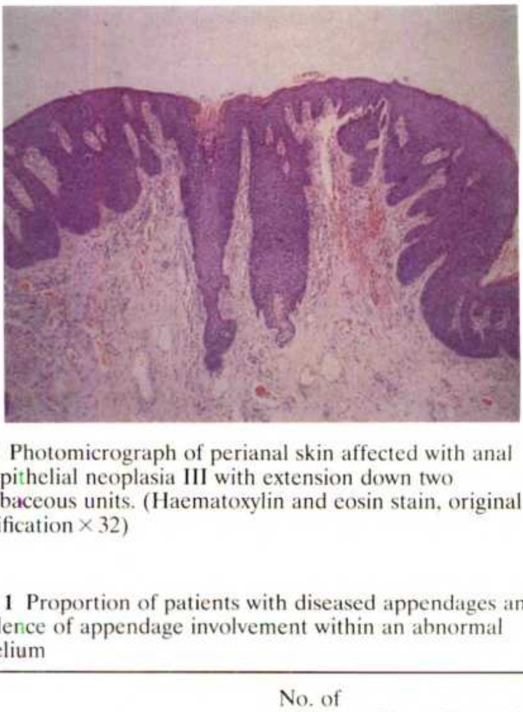

Fig. 2 Photomicrograph of perianal skin affected with anal intraepithelial neoplasia III with extension down two pilosebaceous units. (Haematoxylin and eosin stain, original magnification × 32)

Table 1 Proportion of patients with diseased appendages and prevalence of appendage involvement within an abnormal epithelium

Appendage	No. of patients	No. of patients with appendage involvement	Proportion of diseased appendages*
Hair bulb (below infundibulum)	17	0 (0)	0 (0)
Hair infundibulum	25	14 (56)	79 of 138 (57)
Sweat gland	18	10 (56)	24 of 96 (25)
Sebaceous gland	17	7 (41)	11 of 69 (16)
Eccrine gland	6	0 (0)	0 (0)

Values in parentheses are percentages. *Number of diseased appendages as a proportion of the total number of appendages beneath diseased epithelium

Table 2 Depth of normal skin appendages

Appendage	Depth from keratin–spinosum junction (mm)	Depth from base of adjacent rete peg (mm)
Hair bulb	1·88 (0·65–4·28)	1·76 (0·49–4·17)
Hair infundibulum	0·84 (0·37–2·12)	0·83 (0·19–2·10)
Sweat gland	2·02 (0·86–4·02)	1·92 (0·78–3·72)
Sebaceous gland	1·20 (0·42–2·59)	1·13 (0·28–2·48)
Eccrine gland	2·23 (0·90–3·63)	2·05 (0·82–3·39)

Values are median (range)

Table 3 Depth of disease penetration into appendages for individual patients

Appendage	Depth from keratin–spinosum junction (mm)	Depth from base of adjacent rete peg (mm)
Hair follicle		
Transverse	0·99 (0·57–2·17)	0·91 (0·43–2·10)
Perpendicular	1·04 (0·44–1·94)	1·14 (0·00–1·67)
Sweat gland	1·24 (0·76–2·40)	0·94 (0·50–2·20)
Sebaceous gland	1·60 (1·02–2·40)	1·44 (0·96–1·90)

Values are median (range)

Table 4 Depth of dermal–subcutaneous junction in normal and diseased perianal skin and anal canal

	Depth (mm)	
Origin	Normal	AIN III
Keratin–spinosum junction	2·18 (0·8–5·1)	2·24 (1·88–3·98)
Adjacent rete peg	1·96 (0·7–4·5)	1·72 (1·28–3·41)

Values are median (range)

The median and range depth of normal appendages is shown in *Table 2*. The deepest hair bulb, infundibulum, apocrine sweat glands, sebaceous and eccrine sweat glands in this series were at a median depth of 4·28, 2·12, 4·02, 2·59 and 3·63 mm respectively from the keratin–spinosum junction.

The median depth of the dermal–subcutaneous junction was approximately 1·96 mm below the rete peg with the deepest junction at 4·50 mm. If the deepest appendage were to be obliterated at 4·28 mm, 96 per cent of dermal tissue would also be destroyed.

The median disease penetration of appendages beneath rete pegs was about 1·02 mm but, more importantly, the deepest detectable disease was at 2·20 mm in sweat glands (*Table 3*). Tissue destruction to this level would also destroy a significant amount of normal tissue including 93 per cent of all sebaceous glands (in this sample). It is recognized that sebaceous gland secretions are important to maintain the suppleness of healing skin. Tissue destruction to 2·20 mm would also destroy all dermal tissue in over 50 per cent of patients (*Table 4*).

AIN was associated with a significant increase in the thickness of the perianal and anal canal epithelium (*Table 5*). There was a 50 per cent increase in the thickness of diseased perianal skin and a 100 per cent increase in dysplastic anal canal epithelium. Although there was an increase in the thickness of the transition zone epithelium affected by high-grade disease, the small numbers available ($n = 5$) make statistical analysis difficult. The increase in epithelial thickness may reflect a combination of cellular proliferation, increased cellular size or prolonged cellular survival.

Table 5 Thickness of normal and dysplastic epithelium

	Thickness (mm)		
	Normal	AIN III	*P**
Perianal skin	0·23 (0·14–0·34)	0·36 (0·27–0·67)	<0·0001
Anal canal	0·15 (0·12–0·23)	0·30 (0·15–0·53)	<0·01
Anal transition zone	0·12 (0·08–0·19)	0·17 (0·15–0·27)	>0·05

Values are median (range). *Wilcoxon rank sum test

Discussion

This study has important implications for designing effective ablation treatment for AIN. AIN involved the shafts of anal skin appendages in 19 of 30 patients. The prevalence of AIN in hair follicles and sweat glands was 57 and 25 per cent respectively. AIN significantly increased the thickness of perianal and anal canal epithelium.

The maximum depth of AIN detected in the hair infundibulum, sebaceous and sweat glands was 1·67, 1·90 and 2·20 mm respectively, measured from the base of the adjacent rete peg. Therefore, tissue ablation to at least 2·20 mm below the basement membrane would be required to ensure that all disease was eradicated. Ablation to this depth may negate the benefits of ablation over excision as this depth of tissue destruction would eradicate 93 per cent of sebaceous glands. Sebaceous glands are important for normal healing and their destruction would cause delayed and painful healing. However, the potential depth for disease penetration into the appendages is greater as the deepest hair infundibulum, sebaceous and sweat glands were at 2·10, 2·48 and 3·72 mm respectively. Tissue destruction to 3·72 mm would destroy all sebaceous and sweat glands.

Ablation treatment is attractive and could be performed in outpatients, particularly for small lesions. Ablation treatments have two main problems: destruction of the lesion prevents histopathological examination so identification of microinvasion is impossible[13], and the depth of destruction is uncertain. Larger areas treated by ablation heal by secondary intention which may be slow, painful and result in scarring.

There are two further considerations before applying these data clinically. The measurements were performed on archival tissue blocks and a correction for tissue shrinkage due to processing is therefore needed before *in vivo* application. Shrinkage of between 5 and 20 per cent has been reported[5]. Second, the keratin layer is involved in treatment and, as its depth is variable, the depth of tissue destruction may be measured from adjacent normal epithelium as described previously[11].

The results of this study are similar to data on vulval intraepithelial neoplasia[10,11]. As with vulval intraepithelial neoplasia there was no evidence of intraepithelial neoplasia involving the hair shaft below the infundibulum[9,11]. The infundibulum and hair shaft are immunohistochemically different and this may act as a functional basement membrane to disease penetration. The present study showed an increased prevalence of sweat gland involvement compared with vulval dysplasia but the discrepancy may result from sample variation[11].

This study highlights the subepithelial component of AIN and has implications for subsequent treatment. There has been no previous attempt to assess the distribution of the skin appendages with regard to their position in either the perianal skin or anal canal. The majority of appendages may exist in perianal skin alone; AIN in the anal canal may be confined to epithelium and thus be suitable for ablation. The anal canal does contain exocrine glands which may potentially be affected by disease penetration. Investigation into the distribution of perianal skin and anal canal appendages with sequential tissue sectioning may answer these questions.

In conclusion, since there is involvement of skin appendages in AIN to a depth of 2–3 mm below the basement membrane, ablational treatments are unlikely to eradicate high-grade dysplasia without potentially harmful consequences. There may even be a delay in the diagnosis of early invasive (microinvasive) disease. Thus, it is recommended that excision of high-grade lesions remains the treatment of choice to ensure adequate clearance of disease and allow full histopathological assessment.

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Comparison of three techniques for adrenalectomy

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Background Conventional open adrenal surgery requires relatively large incisions and is associated with postoperative wound pain, intercostal neuralgia and pulmonary complications. Introduction of laparoscopic techniques has enabled development of minimally invasive adrenalectomy.

Methods A case–control study of nine open, nine transperitoneal laparoscopic and 12 retroperitoneal endoscopic adrenalectomies was done in patients who were matched for Quetelet index, adrenal disorder and size of adrenal lesion; all tumours were less than 6 cm in diameter.

Results Conversion to open adrenalectomy was necessary in two patients having transperitoneal laparoscopic adrenalectomy and in one having retroperitoneal endoscopic adrenalectomy. Operative time was longest in transperitoneal laparoscopic adrenalectomy ($P = 0\cdot004$ and $P = 0\cdot005$ *versus* open and retroperitoneal endoscopic adrenalectomy respectively). Blood loss was least in retroperitoneal endoscopic adrenalectomy ($P = 0\cdot01$ *versus* both other groups). End-tidal carbon dioxide increase was greater in transperitoneal laparoscopic and retroperitoneal endoscopic than in open adrenalectomy ($P = 0\cdot014$ and $P = 0\cdot01$ respectively). After retroperitoneal endoscopic adrenalectomy, use of analgesia was least ($P = 0\cdot0003$ *versus* other groups). Postoperative hospital stay was shortest after retroperitoneal endoscopic adrenalectomy ($P = 0\cdot024$ and $P = 0\cdot027$ *versus* open and transperitoneal laparoscopic procedures respectively).

Conclusion Retroperitoneal endoscopic adrenalectomy was optimal in patients with small adrenal tumours.

Conventional adrenal surgery requires relatively large incisions because the adrenal grands are located deeply in the retroperitoneal space. Several authors have recently reported laparoscopic adrenalectomy to be feasible for various conditions such as cortisol- and aldosterone-producing adenomas, Cushing's disease resistant to pituitary surgery or irradiation, incidentaloma and also phaeochromocytoma[1–5]. Small adrenal tumours are conventionally resected through the posterior approach which may involve removal of the 11th or 12th rib[6]. The morbidity after open adrenalectomy includes wound pain, intercostal neuralgia, pneumonia or wound infection (particularly in patients with obesity due to Cushing's syndrome), pulmonary atelectasis and incisional hernia[7].

Since June 1994, a laparoscopic approach to adrenal surgery has been adopted at the authors' institutions for all patients with adrenal tumours less than 6 cm in diameter. After initial experience with laparoscopic transperitoneal adrenalectomy in nine consecutive patients, retroperitoneal endoscopic access to the adrenal gland was used because the transperitoneal laparoscopic approach proved technically difficult and time consuming. The aim of this study was to compare the results of open, endoscopic transperitoneal and retroperitoneal adrenalectomy.

Patients and methods

The medical charts of nine consecutive patients who had adrenalectomy via a dorsal approach at the University Hospital Dijkzigt between February 1992 and June 1994 were reviewed, together with the charts of patients who had either transperitoneal laparoscopic or retroperitoneal endoscopic adrenalectomy at the authors' institutions since.

Full clinical information, operative details and postoperative outcome were recorded. In patients with bilateral disease, the operative time and blood loss per side were documented separately. Analgesic requirement was determined using the Medication Quantification Scale as described by Masters-Steedman *et al.*[8]. The Quetelet index (quotient of body-weight and square of body-length in metres) was determined for all patients.

Operative procedures

Patients with Cushing's syndrome were given corticosteroids during and after operation. Patients with a phaeochromocytoma had α- and β-adrenergic blockade and plasma expansion, when necessary, for at least 10 days before adrenalectomy. The haemodynamics in these patients were monitored at operation using a Swan–Ganz catheter. Antibiotics or drains were not used routinely.

Open adrenalectomy. The patient was placed prone. After an incision extending from the tenth rib to the iliac crest, the sacrospinalis muscle was retracted medially and either the 11th or 12th rib was resected. The adrenal gland was exposed by opening Gerota's fascia. After ligation of the adrenal arteries and the adrenal vein, the adrenal tumour was removed.

Laparoscopic transperitoneal right adrenalectomy. The patient was placed in a supine position with the legs supported in stirrups. After establishment of pneumoperitoneum with a maximum pressure of 14 mmHg, the laparoscope was placed through a 10-mm trocar inserted 2 cm cranially to the umbilicus. The other trocars were placed as shown in *Fig. 1*. Two fan

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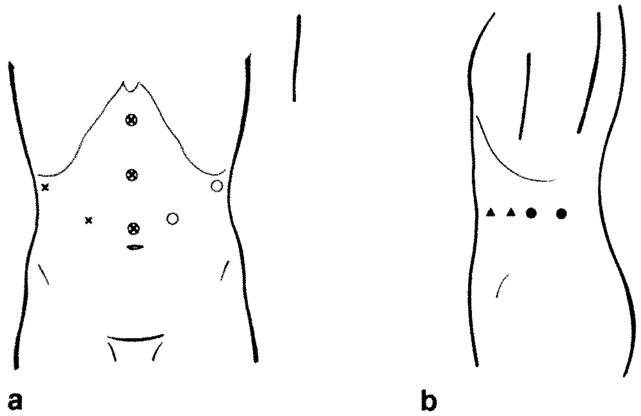

Fig. 1 **a** Trocar position for right (×) or left (○) transperitoneal laparoscopic adrenalectomy. **b** Placement of 10-mm (●) and 5-mm (▲) trocars in left retroperitoneal endoscopic adrenalectomy

retractors were used to retract the liver cranially and the duodenum medially. The peritoneum overlying the adrenal was opened and after identification of the right adrenal gland, the adrenal vein was clipped and divided. The adrenal arteries were either diathermied or clipped and divided. After dissection, the adrenal gland was placed in a plastic bag and removed.

Laparoscopic transperitoneal left adrenalectomy. The positioning of the patient was similar to that for laparoscopic transperitoneal right adrenalectomy. Placement of the trocars is shown in *Fig. 1*. After identification of Treitz ligament, the transverse colon was retracted cranially and the left colon laterally using fan retractors. The peritoneum of the mesocolon was opened laterally to the inferior mesenteric vein. Elevation of the inferior border of the pancreas revealed the left adrenal gland. After clipping the left adrenal vein and adrenal arteries, the adrenal gland was placed in a plastic bag and removed.

Endoscopic retroperitoneal adrenalectomy. The patient was placed in a lateral decubitus position. Through a muscle splitting incision of 2 cm in the mid-axillary line just caudal to the tip of the 11th rib, a dissecting balloon (Origin; Medsystems, Menlo Park, California, USA) was introduced to create a retroperitoneal space (*Fig. 2*). After replacement of the balloon by a trocar, carbon dioxide was insufflated to a maximum pressure of 12 mmHg and the laparoscope introduced. The other trocars were placed as shown in *Fig. 1*. The kidney was identified by incising Gerota's fascia. Cranial dissection revealed the adrenal gland. If necessary, an additional trocar was inserted to allow retraction of the right lobe of the liver, in right adrenalectomy, or the peritoneum when this was lacerated. The adrenal vein and the adrenal arteries were clipped and divided. The adrenal was placed in a bag and removed.

Statistical analysis

To compare the characteristics of the patients and the results of the three operative techniques, all data were recorded on a database. The median values and standard errors of the continuous variables were calculated. To analyse dichotomous variables, the Pearson χ^2 test was performed. For analysis of the continuous variables, the Mann–Whitney U test was used. Analysis of patients who had either transperitoneal laparoscopic or retroperitoneal endoscopic adrenalectomy but required conversion to open adrenalectomy was performed on the basis of the intention to treat. Statistical comparisons were made between all three techniques (open *versus* transperitoneal, open *versus* retroperitoneal, transperitoneal *versus* retroperitoneal). A P value lower than 5 per cent was interpreted as a significant difference between two techniques.

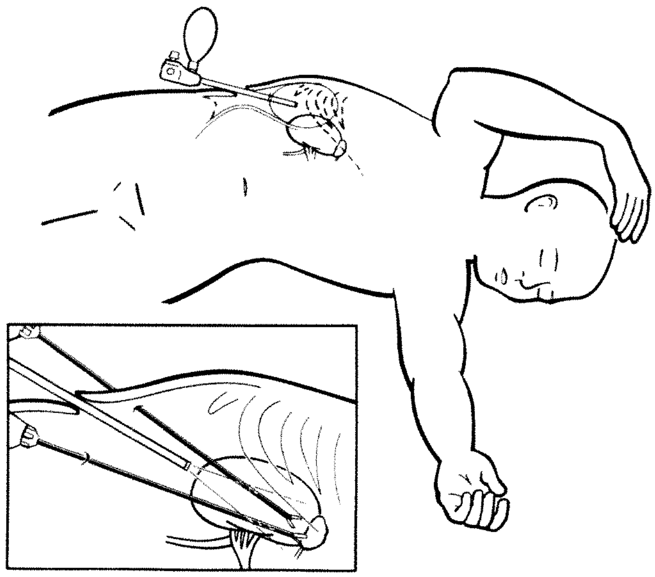

Fig. 2 Right retroperitoneal endoscopic adrenalectomy. Balloon dilatation of the right retroperitoneal space with the patient in the lateral decubitus position

Results

The patients' age, Quetelet index, diagnosis, side of the adrenal lesion and diameter of the adrenal tumour were similar in the three groups (*Table 1*). Histological examination of the incidentalomas showed an adrenal cyst, adenomyosis, nodular hyperplasia and haemorrhage in the adrenal gland in one case each. Two patients had bilateral adrenal disease. One had Cushing's disease resistant to pituitary surgery and irradiation. The other had bilateral phaeochromocytomas associated with neurofibromatosis. Both patients with bilateral disease had retroperitoneal endoscopic adrenalectomy. All other patients had unilateral adrenal disease.

The operative time of open adrenalectomy and endoscopic retroperitoneal adrenalectomy was similar but less than that for transperitoneal laparoscopic adrenalectomy (*Table 2*). Peroperative blood loss was lowest following the retroperitoneal method. The end-tidal carbon dioxide increased more during endoscopic or laparoscopic adrenalectomy than during open adrenalectomy. The increase of end-tidal carbon dioxide was similar during the transperitoneal and retroperitoneal

Table 1 Clinical details of patients having adrenalectomy

	Open	Trans-peritoneal	Retro-peritoneal
No. of patients	9	9	10
Age (years)	36(4)	44(6)	46(5)
Quetelet index (kg/m^2)	24·5(1·8)	24·5(0·6)	23·6(1·2)
Cushing's adenoma	4	2	6
Conn's adenoma	3	4	2
Phaeochromocytoma	0	0	3
Incidentaloma	2	1	1
Virilizing tumour	0	2	0
Side of lesion (L/R)	7/2	4/5	6/6
Diameter of adrenal tumour (cm)	3·0(0·2)	3·0(0·3)	4·0(0·5)

Values are median(s.e.)

Table 2 Comparison of operative details for different methods of adrenalectomy

	Open	Trans-peritoneal	Retro-peritoneal
Operative time (min)	60(6)**	150(10)†	75(13)
Blood loss (ml)	175(44)‡	150(125)‡	20(86)
End-tidal carbon dioxide gradient (%)	0·2(0·1)‡,††	0·5(0·1)	0·7(0·2)
Postoperative analgesia	34(12)*	20(4)*	6(1)
Postoperative hospital stay (days)	6·0(0·3)§	6·0(1·0)¶	4·0(1·0)

Values are median(s.e.). *P = 0·0003, †P = 0·005, ‡P = 0·01, §P = 0·024, ¶P = 0·027 *versus* retroperitoneal; **P = 0·004, ††P = 0·014 *versus* transperitoneal. Mann–Whitney U test

approaches. The use of postoperative analgesia was least after retroperitoneal endoscopic adrenalectomy. Postoperative hospital stay was shortest following endoscopic retroperitoneal adrenalectomy.

Intraoperative complications did not occur in patients who had open adrenalectomy. Two patients complained of a burning pain in the flank for 7 and 14 months after open adrenalectomy.

Two transperitoneal adrenalectomies required conversion to laparotomy because of bleeding from the right adrenal vein and failure to identify a cortisol-producing adrenal tumour on the left side. Postoperative complications were recorded in two patients who had a transperitoneal adrenalectomy. One developed a *Staphylococcus aureus* sepsis due to phlebitis; another developed a transient fever of unknown cause after operation and recovered spontaneously.

In the retroperitoneal endoscopic adrenalectomy group, conversion to lumbotomy was necessary in a patient with a phaeochromocytoma 3 cm in diameter, with dense vascular adhesions to surrounding tissues.

In the two patients with phaeochromocytoma, intraoperative systolic blood pressure did not exceed 150 mmHg. The intraoperative pulse rate remained below 140 beats per min in both patients.

Tears of the peritoneum occurred in six of 12 retroperitoneal procedures. Retraction of the peritoneum with either a fan retractor or an endoscopic clamp sufficed to maintain a good view of the operative field.

Discussion

The adrenal gland can be approached endoscopically both transperitoneally and retroperitoneally. The transperitoneal approach can be performed with the patient either in a supine position or a lateral decubitus position (flank approach)[9]. In the authors' experience with the transperitoneal supine approach, retraction of organs surrounding the adrenal glands is cumbersome and identification, particularly of the left adrenal, can be difficult. The flank approach, as advocated by Gagner *et al.*[9], requires less dissection but the average operating time is 2·3 h, which appears longer than that for the retroperitoneal endoscopic approach.

The retroperitoneal endoscopic approach to the adrenal glands is based on the technique of pneumography which was developed in the 1970s[10]. In pneumography, the retroperitoneal space is insufflated with air to outline the kidney and the adrenal to allow radiographic imaging of renal or adrenal tumours. In retroperitoneal endoscopic adrenalectomy, retroperitoneal insufflation with carbon dioxide creates a working space and provides retraction of either liver or pancreas. Although anatomical landmarks appear scarce in the retroperitoneal space, identification of psoas muscle and kidney is always possible. Opening Gerota's fascia and subsequent cephalad dissection reveals the adrenal gland. In retroperitoneal endoscopic adrenalectomy, trocars should be placed close to the tips of the 11th and 12th ribs to allow sufficient manoeuvring space for the endoscopic instruments. The retroperitoneal endoscopic approach to the adrenals is not hampered by intraperitoneal adhesions from previous abdominal surgery, another advantage over transperitoneal laparoscopic access.

Concern existed that insufflation of the retroperitoneal space might cause hypercarbia[1]. However, in this study the increase in end-tidal carbon dioxide during retroperitoneal endoscopic adrenalectomy was similar to that observed in transperitoneal endoscopic adrenalectomy. This is in accordance with an experimental study by Chiu *et al.*[11] in pigs, in which greater systemic and renal haemodynamic alterations were found during pneumoperitoneum than during pneumoretroperitoneum.

Mercan *et al.*[12] performed endoscopic retroperitoneal adrenalectomy with the patient in the prone semijackknife position. The authors prefer the lateral decubitus position because it allows easier access to the abdomen if conversion to open adrenalectomy is necessary. The disadvantage of turning the patient in bilateral adrenal disease seems limited because this required less than 15 min in the present study.

Endoscopic treatment of patients with a phaeochromocytoma is controversial because of the possible multiplicity of the tumour and the risk of an intraoperative hypertensive crisis. Use of the endoscopic technique precludes thorough exploration of the para-aortic region and the contralateral adrenal gland. However, scintigraphy with [^{131}I]meta-iodobenzylguanidine, computed tomography (CT) and magnetic resonance imaging of the abdomen localize phaeochromocytomas very precisely[13,14]. As a result of continuing improvement of imaging studies, several authors have concluded that the extraperitoneal dorsal or flank approach is justified in patients with phaeochromocytomas smaller than 6 cm in diameter[15,16]. Manipulation of phaeochromocytomas can cause intraoperative hypertension. Although the authors' endoscopic experience with phaeochromocytoma is limited to two patients, hypertension did not occur. The endoscopic approach to small phaeochromocytomas is considered suitable. Concern might exist about retroperitoneal insufflation of carbon dioxide in phaeochromocytoma because fatalities occurred when pneumography was undertaken as the standard form of imaging in this condition. However, these fatalities were seen in patients who had not received α- and β-adrenergic blockade before pneumography. In patients with a phaeochromocytoma, combined α- and β-adrenergic blockade remains an essential measure before undertaking procedures that entail manipulation.

Debate exists on the size limit of adrenal tumours suitable for endoscopic removal. Adrenal tumours with a high suspicion of malignancy should not be considered for endoscopic removal because the role of laparoscopic techniques in the treatment of malignant tumours remains controversial[17]. Differentiation between benign and malignant adrenal tumours does not appear relevant in patients with aldosterone-producing tumours because malignancy in Conn's syndrome is extremely rare[18]. Patients with cortisol-producing autonomous adrenocortical tumours with concordant CT images and $[^{131}\mathrm{I}]6\beta$-'iodomethyl-19-norcholesterol scintigraphy seldom have malignant adrenal tumours[19]. In cases of discordance between these two imaging modalities, the risk that a cortisol-producing adrenal tumour less than 6 cm in diameter is malignant is one in 10 000[20].

Preoperative differentiation between benign and malignant phaeochromocytoma is impossible. Limiting endoscopic adrenalectomy to phaeochromocytomas less than 6 cm in diameter appears appropriate since radical resection of such small tumours is possible endoscopically. Gajraj and Young[21] demonstrated that malignancy was uncommon in adrenal incidentalomas with a diameter less than 6 cm. Therefore, endoscopic adrenalectomy also seems a safe procedure for the removal of adrenal incidentalomas with a diameter less than 6 cm.

The endoscopic retroperitoneal approach to adrenal tumours less than 6 cm in diameter may become the method of choice because intraoperative blood loss, postoperative pain and hospital stay are less than for open or transperitoneal laparoscopic adrenalectomy, without prolonging the duration of operation.

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Short note

Incidence of Meckel's diverticulum in Turkey

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Meckel's diverticulum is the most common anomaly of the human gastrointestinal tract. The incidence varies from 0·3 to 3·0 per cent in the general population, but a 2 per cent incidence is commonly accepted[1]. When Meckel's diverticulum is found incidentally, some propose its routine removal[1,2], whereas others prefer to leave the non-complicated diverticulum alone[3,4]. There is still controversy over two points that are unclear: the incidence and lifetime risk of complications from Meckel's diverticulum. A prospective multicentre study was conducted to ascertain the incidence and characteristics of Meckel's diverticulum in Turkey.

Patients and methods

Contributing centres were asked to record the name, age and sex of any adult patient in whom a Meckel's diverticulum was encountered during laparotomy for any cause, the indication for laparotomy, the size of the diverticulum and the distance from the terminal ileum. Surgeons were asked to look for the presence of Meckel's diverticulum by inspecting the small intestine throughout its entire length.

The main purpose was to determine the incidence of Meckel's diverticulum. When the estimated value was taken as 2 per cent and hypothesized incidence as 1 per cent, the sample size required was 1920 for $\alpha = 0{\cdot}05$ and $\beta = 0{\cdot}05$, when calculated with one-proportion hypothesis testing. The obtained incidence was compared with the assumed incidence of 2 per cent by the hypothesis test for sample proportion *versus* hypothesized value.

Results

Records of 2559 patients (1474 men and 1085 women aged 18–94 years) were obtained from 14 participating centres. One patient operated on for Meckel's diverticulitis was excluded. Thirty-four Meckel's diverticula were encountered amongst 2558 patients (1·3 per cent). None of these non-complicated diverticula was excised and no patient had a previous history of Meckel's diverticulectomy.

The male:female ratio was 2·1:1. Meckel's diverticula were located 30–100 (median 65) cm proximal to the ileocecal valve and their length ranged from 1 to 8 (median 3) cm.

When the obtained incidence of 1·3 per cent was compared with the assumed incidence of 2 per cent, the difference was highly significant ($z = -2{\cdot}53$, $P = 0{\cdot}006$).

Discussion

It is widely stated that Meckel's diverticulum is seen twice as frequently in males as in females. This has been recorded in patients with complicated Meckel's diverticulum. However, in this study, the same ratio (2·1:1) was found in the general population, which may imply that the complication rate is the same for both sexes.

The proper treatment of incidentally found Meckel's diverticulum is controversial. Soltero and Bill[3] estimated the lifetime risk of complications from a Meckel's diverticulum to be 4·2 per cent, with the risk decreasing throughout life. Others have also estimated the risk to be low and proposed leaving the incidentally found Meckel's diverticulum in place, assuming that the risk of complications from its surgical removal is higher[4]. On the other hand, Cullen *et al.*[1] estimated the lifetime risk as 6·4 per cent and operative mortality and morbidity rates as 1 and 2 per cent, respectively. While the operative morbidity and mortality rates are much higher for diverticulectomy for complicated Meckel's diverticulum, routine removal is proposed when encountered[1,2].

In these estimations, a 2 per cent incidence is assumed in the general population. However, this study, and previous larger studies, have shown a lower incidence of Meckel's diverticulum. In this case, when Meckel's diverticulum is considered to be a relatively rarer entity than assumed, the complications encountered become even more serious. Thus, when the lifetime complication risks are calculated for a lower incidence by statistical methods, the complication rate and the overall lifetime risks increase in the presence of Meckel's diverticulum. This finding supports those in favour of routine removal.

In this study, the incidence of Meckel's diverticulum was found to be lower than that generally anticipated. The estimated lifetime complication risks for a 2 per cent incidence of Meckel's diverticulum increase when corrected for a 1·3 per cent incidence and, therefore, routine removal of Meckel's diverticulum may be warranted when encountered during laparotomy.

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Short note

Herniography for groin pain of uncertain origin

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While computed tomography, laparoscopy, barium series, urography and ultrasonography have all been used to demonstrate a groin hernia, herniography (peritoneography) was initially developed to demonstrate hernias in a paediatric population and has subsequently attracted attention for the investigation of adult patients with groin pain of uncertain aetiology[1–3]. Herniography is simple to perform, inexpensive and requires no additional equipment to that available in most radiology departments. It can reliably establish the diagnosis of hernia before surgery[1–3]. Potential complications are rare but include discomfort during the procedure, reaction to the radiographic contrast, abdominal wall haematoma[2], intravascular injection and injection into or damage to intra-abdominal organs[4]. This study examined the current role of herniography in the investigation of groin pain.

Patients and methods

Herniography was performed as an outpatient procedure lasting 20 min on 18 male and 16 female patients with an age range of 20–70 (median 47) years and who had groin pain of uncertain origin. After voiding the urinary bladder, a pneumoperitoneum needle was introduced under local anaesthesia into the left lower quadrant at the lateral border of rectus abdominis. Under fluoroscopic screening, 50 ml non-ionic water-soluble contrast was introduced into the peritoneal cavity, the patient was placed prone in a head-up position and contrast was allowed to drain, with the assistance of repeated Valsalva manoeuvres, into the inguinal fossae related to the umbilical ligaments.

Results

An inguinal hernia was found in ten of the 34 patients who underwent herniography; there were six direct (*Fig. 1*), two indirect and one bilateral indirect hernias, one diffuse groin weakness and one femoral hernia; the patient with a femoral hernia also had a direct inguinal hernia. Following appropriate surgery, one patient has suffered persistent groin pain and nine (including one patient who developed a postoperative wound infection) are asymptomatic. Of the 24 patients with normal herniography, eight were reassured and are now pain free, eight have attracted other diagnoses (adductor tendonitis, nerve entrapment, saphenovarix, endometriosis), five remain symptomatic and under review without a definitive diagnosis, two have been lost to follow-up and one patient has died from an unrelated cause.

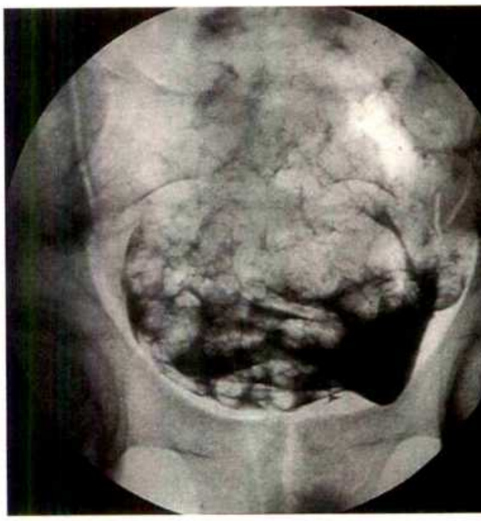

Fig. 1 Herniogram demonstrating left direct inguinal hernia

Discussion

In re-evaluating the technique of herniography for groin pain of uncertain cause, ten of 34 patients had an unexpected hernia diagnosed while in 24 herniography avoided unnecessary groin exploration and the potential attendant morbidity. This series confirmed previous studies in which 33–45 per cent of patients[1–3] have had a hernia demonstrated as the cause of unexplained groin pain. There were no false-positive examinations (herniography positive, no hernia at operation) in this or other series[1–3] and false-negative herniograms (herniography normal, hernia at operation) apparently do not occur[1], although in theory a sliding hernia or an incarcerated hernia could be more difficult to demonstrate[1].

Herniography is also useful in the diagnosis of recurrent groin hernias[2], although 33 of 34 patients in this study had not undergone previous groin surgery. In patients with symptoms suggestive of a hernia but with normal physical examination, blind exploration may no longer be acceptable for ethical or fiscal reasons, particularly as many patients with a normal herniogram become symptom free on follow-up[3].

Herniography has not been widely adopted, despite extensive experience in selected centres. Herniography may circumvent the limitations of physical examination of the groin and the difficulties associated with other invasive and non-invasive techniques but would merit formal comparison with those techniques. Herniography should no longer be branded 'a diagnostic procedure in search of a need'[5]. Used judiciously, before surgery when diagnostic uncertainty remains, herniography is a diagnostic aid which may identify the presence of a hernia after equivocal physical examination, demonstrate bilateral hernias (perhaps suitable for laparoscopic mesh repair) or prevent unnecessary groin exploration.

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Case report

Acute stomal 'contact' dermatitis or pemphigus

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Karaya (Hollister, Wokingham, UK) and Stomahesive (ConvaTec, Uxbridge, UK) are both widely used sealants for stoma appliances. Fortunately they are hypoallergenic and severe cutaneous reactions are rare.

Case report

A 65-year-old man presented with acute left-sided malignant large bowel obstruction. At laparotomy, as there was extensive local spread and multiple hepatic deposits, he was palliated with a loop transverse colostomy.

The following day the patient developed superficial blistering around the stoma site (*Fig. 1a*). An initial diagnosis of contact dermatitis appeared to be confirmed when similar skin lesions were seen at patch test sites for Micropore (3M Healthcare, Loughborough, UK), Opsite (Smith and Nephew Healthcare, Hull, UK), Stomahesive and Granuflex (Convatec), but not Karaya. Over the following 6 days a variety of stomal appliances and dressings were tried, but the skin erosions spread relentlessly (*Fig. 1b*). Only at this time was pemphigus vulgaris suspected. This diagnosis was confirmed when biopsies demonstrated classical histological and immunofluorescence features, and pemphigus antibodies were detected in the serum. The skin blistering completely resolved with high-dose oral steroids but the patient died 14 days later while the steroids were being reduced.

Discussion

Parastomal skin irritation is common and may indeed be disabling[1] but acute contact dermatitis to stomal sealants is rare as they are hypoallergenic.

Immunobullous diseases have historically been linked with many underlying malignancies[2] but the evidence for such an association is conflicting[3–5]. This appears to be the first description of pemphigus vulgaris precipitated by surgery. The repeated changing of dressings, each fixed with adhesive tape, led to the development of new lesions in the locally traumatized skin (Koebner phenomenon). This necessitated use of ever larger dressings and gave the illusion of a spreading 'dermatitis'.

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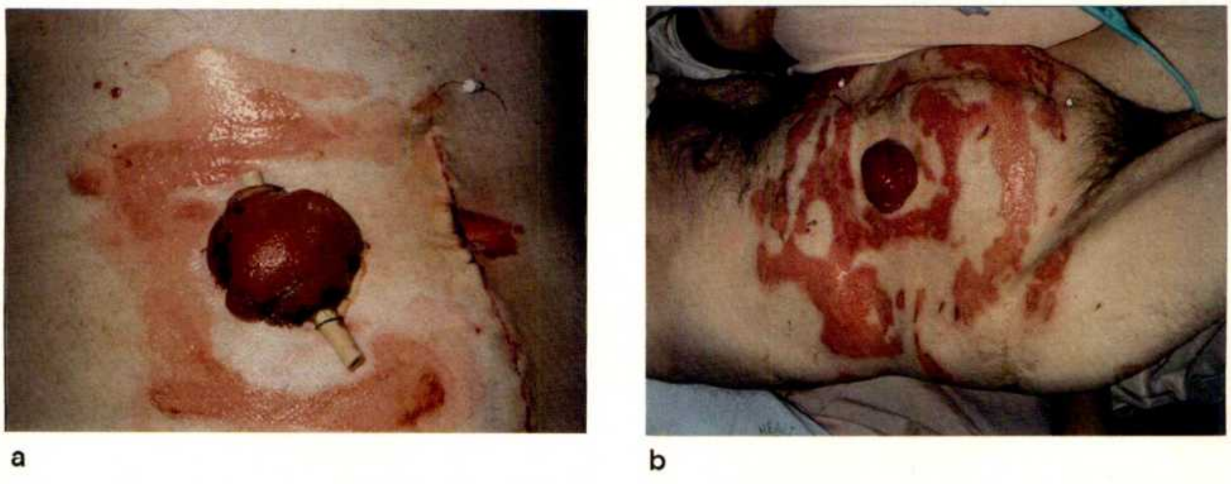

Fig. 1 **a** Peristomal blistering that appears to spare the Stomahesive contact area. **b** Appearance on day 6, showing widespread skin fragility and erosive lesions

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Effect of fundoplication on transient lower oesophageal sphincter relaxation and gas reflux

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Background Fundoplication is used widely to treat severe gastro-oesophageal reflux disease. Difficulty in belching and increased flatulence are common side-effects. Transient lower oesophageal sphincter (LOS) relaxation is important to help vent gas from the stomach. The effect of fundoplication on LOS function and gas reflux was therefore investigated.

Methods Oesophageal manometry was performed before operation and 3–15 months after fundoplication in 14 patients with reflux disease who had a total (360°) fundoplication. Five patients also had highly selective vagotomy. Gastric distension was induced by 750 ml carbon dioxide.

Results Fundoplication reduced the median number of episodes of gas reflux during 10 min of gastric distension from 5 (interquartile range (i.q.r.) 3–7) to 0 (i.q.r. 0), and the median number of transient LOS relaxations from 4 (i.q.r. 2–6) to 0 (i.q.r. 0–1). Fundoplication did not affect basal LOS pressure but significantly increased nadir pressure during swallow-induced relaxation.

Conclusion Fundoplication controls reflux by inhibiting the triggering of transient LOS relaxation and by preventing the complete ablation of pressure at the gastro-oesophageal junction during LOS relaxation. These effects may also contribute to the side-effects of the operation.

Fundoplication is used widely to treat severe gastro-oesophageal reflux disease. The operation provides good long-term control of reflux[1]. The mechanism of action of fundoplication, however, remains incompletely understood. Fundoplication increases the resting pressure at the gastro-oesophageal junction and the length of the high-pressure zone[1,2], but the significance of these findings has been questioned[3].

The authors have shown that fundoplication reduces postprandial reflux by affecting the frequency of transient lower oesophageal sphincter (LOS) relaxation and rendering LOS relaxation incomplete[4]. Common side-effects reported after the operation are difficulty in belching and increased flatulence[1], and the ability to belch has been reported to be reduced[5]. Because transient LOS relaxations are important to vent gas from the stomach[6], the effect of fundoplication on the motor patterns at the gastro-oesophageal junction during gaseous distension of the stomach was investigated.

Patients and methods

Patients

The study included eight women and six men aged from 33 to 70 (mean 47) years who were undergoing fundoplication. All patients had either intractable reflux symptoms that were not controlled by medical therapy or did not want to take antireflux medication long term. Preoperative endoscopy showed normal oesophageal mucosa in four patients, erosive or ulcerative oesophagitis in eight patients and Barrett's oesophagus in two patients. The patients with no endoscopic evidence of oesophagitis all had excessive levels of oesophageal acid exposure (duration below pH 4 of more than 5 per cent). No patient had undergone previous gastric or oesophageal surgery. All patients gave written informed consent and the study was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

Fundoplication

A transabdominal 360° fundoplication was performed by mobilization of the distal oesophagus and the gastric fundus, including ligation of the short gastric vessels. A 50-Fr bougie was placed in the oesophagus, and the fundus was wrapped around the oesophagus and sutured. A 3-cm 'floppy' fundoplication was thus created so that two fingers could be passed through the fundoplication. The hiatus was not sutured. In five patients, highly selective vagotomy was performed before mobilizing the fundus and the oesophagus.

Oesophageal manometry

Oesophageal manometry was performed before operation and 3–15 months after surgery with a 12-lumen catheter assembly (diameter 5·6 mm) that incorporated four 6-cm sleeve sensors[7] radially orientated at 90° to each other to monitor LOS pressure. Intragastric pressure was recorded by a side hole located 1 cm beyond the distal margin of the sleeves. Side holes at the proximal sleeve margin and 4, 8, 12 and 16 cm more proximally recorded motility in the oesophageal body and a side hole in the pharynx monitored swallowing. The sleeves and gastric and oesophageal side holes were perfused with distilled water at a rate of 0·6 ml/min by a low-compliance pneumohydraulic capillary infusion system. The pharyngeal side hole was perfused at a rate of 0·3 ml/min to obtain an accurate indication of the occurrence of swallowing but to minimize the effect of the assembly on the swallow rate. Each lumen was connected to external pressure transducers (Deseret Medical, Sandy, Utah, USA) whose output was displayed on a 12-channel polygraph (Model 7D, Grass Instruments, Quincy, Massachusetts, USA) at a paper speed of 2·5 mm/s.

Study protocol

Oesophageal manometry was performed after a 4-h fast and, in smokers, after abstinence from smoking for at least 6 h. Drugs that might affect oesophageal motility were discontinued for 24 h before the study. After topical anaesthesia of the nostril, the catheter was introduced nasally and positioned with the sleeves straddling the LOS; the patients were then allowed to accommodate to the tube for 15 min. The patients were studied

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in the supine, right lateral and sitting positions. In each position, basal LOS pressure was recorded for 5 min after which five water swallows were performed. After the water swallows, 10 min of basal recording was performed in the sitting position. The stomach was distended abruptly with 750 ml carbon dioxide by instilling a two-part radiological mixture (Fields Negative C; Fields Group Chemicals, Sydney, Australia) into the stomach through the manometric assembly[8]. After distension, recordings were continued for a further 10 min.

Data analysis

Basal end-expiratory pressure at the gastro-oesophageal junction was referenced to intragastric pressure and determined by taking a visual mean of each minute of basal pressure recording. The mean value of the pressure in the four sleeves was calculated and the grand mean value for the 5 min was obtained for each patient. The completeness of relaxation at the gastro-oesophageal junction during water swallows was determined by taking the difference between the nadir pressure during relaxation and the intragastric pressure. The mean values for the four sleeves and for the five swallows were determined.

The recordings were analysed for the occurrence of gas reflux as indicated by the occurrence of oesophageal common cavities[6]. For the purpose of this study, a common cavity was defined as an abrupt increase in intraoesophageal pressure to intragastric pressure in at least the two distal oesophageal recording sites. The patterns of pharyngeal and oesophageal motor function just before, and at the time of the onset of the common cavity, were analysed using criteria applied previously[9]. The recordings were also analysed for transient LOS relaxation. For preoperative studies, transient LOS relaxation was defined as a sudden drop in pressure at the gastro-oesophageal junction of more than 5 mmHg to within 2 mmHg of intragastric pressure, lasting longer than 5 s, which was not accompanied by a pharyngeal swallow signal within 5 s before onset until the relaxation was complete. For the postoperative studies, transient LOS relaxations were scored if the nadir pressure during relaxation was on or below the residual relaxation pressure determined during the water swallows. Separate note was made of transient relaxations whose nadir pressure reached below 2 mmHg relative to intragastric pressure during the postoperative studies[4].

Statistical analysis

Data were analysed using two-way analysis of variance and Student's *t* test. $P<0{\cdot}05$ was judged to be statistically significant.

Results

Eleven of the 14 patients reported complete relief of reflux symptoms after operation; the other three reported only mild heartburn (less than once per week). Four patients complained of mild dysphagia for solids and eight experienced mild bloating.

Basal LOS pressure was not affected significantly by fundoplication or body position (*Fig. 1*). However, fundoplication significantly increased the nadir LOS pressure during water swallows ($P<0{\cdot}0005$; *Fig. 2*). Nadir LOS pressure was also significantly higher in the supine and right lateral positions than in the sitting position, both before and after fundoplication ($P<0{\cdot}02$).

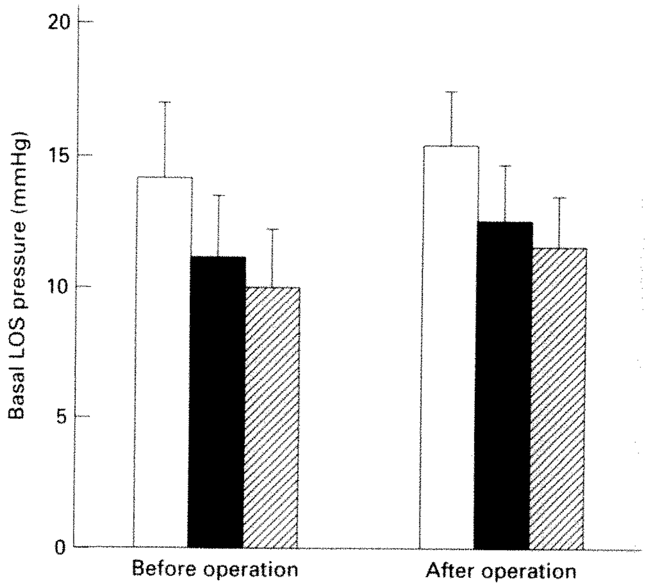

Fig. 1 Mean(s.e.m.) basal lower oesophageal sphincter (LOS) pressure before and after fundoplication. □, Supine; ■, right lateral; ▨, sitting. The differences are not statistically significant. ANOVA

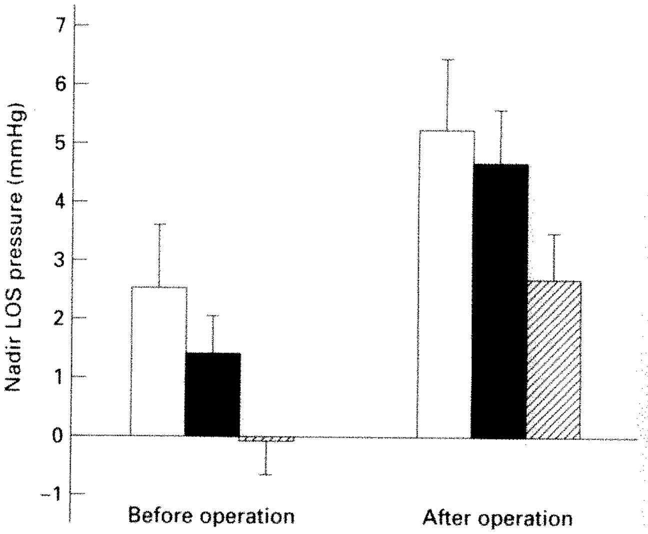

Fig. 2 Mean(s.e.m.) nadir lower oesophageal sphincter (LOS) pressure during water swallows before and after fundoplication. □, Supine; ■, right lateral; ▨, sitting. Effect of operation $P<0{\cdot}0005$, effect of position $P<0{\cdot}02$, ANOVA

Fundoplication almost eliminated gas reflux and reduced the rate of common cavities from median 5 (interquartile range (i.q.r.) 3–7) per 10 min to 0 (i.q.r. 0) per 10 min ($P<0{\cdot}01$; *Fig. 3*). A total of 74 common cavities were recorded before operation. Of these, the majority occurred either during swallow-induced LOS relaxation (40 common cavities) or transient LOS relaxation (31 common cavities, 19 of which occurred in one patient); only three occurred during sustained periods of absent LOS pressure. After operation, only four common cavities were recorded, all of which occurred during transient LOS relaxation.

Fundoplication also substantially reduced the occurrence of transient LOS relaxations during gastric distension, the rate falling from 4 (i.q.r. 2–6) per 10 min before operation to 0 (i.q.r. 0–1) per 10 min ($P=0{\cdot}0001$; *Fig. 4*). Overall, only four transient LOS relaxations occurred after operation (one in each of four patients), all of which had nadir pressures of 2 mmHg or less.

Five of the patients had undergone concomitant highly selective vagotomy. None of these patients had transient LOS relaxations or common cavities, and basal LOS pressure and nadir pressures during LOS relaxations were similar to those in the patients without vagotomy.

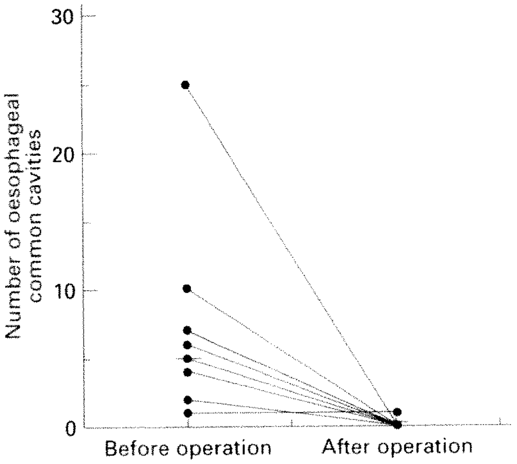

Fig. 3 Number of oesophageal common cavities during 10 min of distension of the stomach with 750 ml carbon dioxide before and after fundoplication. Each point represents the value for an individual patient. The horizontal bars indicate median values. $P < 0.01$ (before *versus* after operation), Mann–Whitney *U* test. LOS, lower oesophagel sphincter

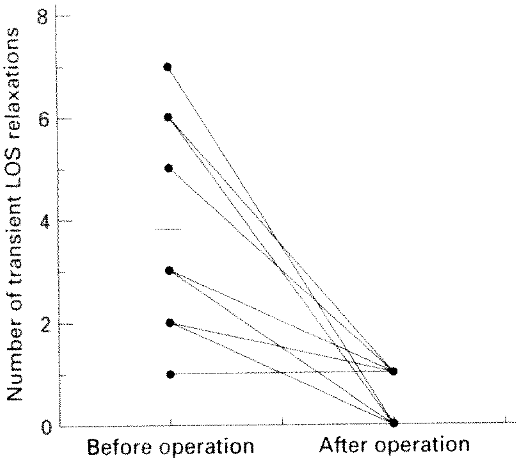

Fig. 4 Number of transient lower oesophageal sphincter (LOS) relaxations during 10 min of distension of the stomach with 750 ml carbon dioxide before and after fundoplication. Each point represents the value for an individual patient. The horizontal bars indicate median values. $P = 0.0001$ (before *versus* after operation), Mann–Whitney *U* test

Discussion

The ability to vent swallowed gas from the stomach is an important physiological function of the LOS. Loss of this function may lead to symptoms resulting from an increased amount of gas in the digestive tract. In normal subjects, gas reflux and belching occur almost exclusively during either transient or swallow-induced LOS relaxation[6]; although absent basal LOS pressure becomes an important mechanism in some patients with reflux oesophagitis[10]. The present study shows that total fundoplication profoundly suppresses gas reflux by inhibiting all of these mechanisms. This finding provides an explanation for some of the side-effects that are reported following fundoplication. A recent study has shown that more than one-third of patients had difficulty in belching and almost half of the patients had flatulence 5 years after the operation[1].

Two factors could have potentially influenced the rate of scored transient LOS relaxations artefactually. First, in this series, as in previous studies[4,11], fundoplication rendered swallow-induced LOS relaxation incomplete, presumably by mechanical compression of the LOS segment. The definition of transient LOS relaxation was therefore modified in the postoperative recordings on the basis that nadir pressure at the gastro-oesophageal junction during swallowing represented complete LOS relaxation. Despite this more liberal definition, very few transient LOS relaxations occurred after operation. Second, there was some concern that patients would experience greater discomfort after fundoplication and swallow more frequently. The greater the swallow rate, the greater the likelihood of a chance association between a swallow and a transient LOS relaxation resulting in the relaxation being classified as swallow-induced, thereby leading to underscoring of transient LOS relaxations. However, the patients were generally more troubled by gastric distension and swallowed more frequently in the preoperative studies because of prolonged periods of oesophageal distension as a result of frequent gas reflux.

Five of the patients had highly selective vagotomy added to the fundoplication. Whether or not this procedure might have influenced the results is difficult to determine but it had no appreciable effect over and above that of the fundoplication. The results of highly selective vagotomy on LOS pressure in humans are conflicting. It does not appear to affect basal LOS pressure[12-14], or LOS relaxation in patients without dysphagia[15]. Although an achalasia-like syndrome has been reported anecdotally[16,17], this effect was transient and was not clearly related to interference with the nerve supply to the LOS. Potentially, highly selective vagotomy could interfere with the sensory arm of the reflex arc that has been postulated to underly triggering of transient LOS relaxations by gastric distension[18,19]. However, reports of the effects of highly selective vagotomy on proximal gastric motility have been conflicting; two studies report a decrease in proximal gastric compliance[20,21] and one found no effect in patients without symptoms[22].

The findings of this study support the authors' previous observations on postprandial reflux[4] that inhibition of transient LOS relaxations is an important mechanism underlying the antireflux effects of fundoplication. In the previous study, the frequency of transient LOS relaxation was reduced by half, whereas in the present series the reduction was over 90 per cent. The reason for the more pronounced effect is not clear but may relate to differences in the method and perhaps pattern of gastric distension, and the longer period of observation in the postprandial study. The mechanism by which fundoplication inhibits the triggering of transient LOS relaxations is not known but may involve the buttressing effect of the fundal wrap on the distensibility of the gastric cardia, the most potent area for triggering of transient LOS relaxation[12].

It was shown previously[4] that part of the antireflux effect of fundoplication appeared to be due to prevention of complete ablation of pressure at the gastro-oesophageal junction during LOS relaxation. In the present study it is not possible to draw any firm conclusion on this effect as the numbers of transient LOS relaxations and episodes of gas reflux after operation were too few. Nevertheless, the finding that fundoplication also abolished gas reflux during swallow-induced LOS relaxation is consistent with this view.

Absent basal LOS pressure appears to be an important mechanism of reflux in a small subset of patients[23], particularly those with severe oesophagitis[9,24]. As with a previous study of postprandial reflux, the authors did not observe gas reflux as a result of sustained absence of basal LOS pressure after fundoplication. This finding suggests that in the process of preventing complete LOS relaxation, fundoplication also maintains a minimal basal pressure at the gastro-oesophageal junction that is sufficient to prevent reflux occurring when intrinsic basal LOS pressure is absent.

Numerous studies have shown that fundoplication increases basal LOS pressure[1,2,25]. This effect, however, is not seen in patients in whom preoperative basal LOS pressure is normal or high. An increase in basal LOS pressure after fundoplication was not observed perhaps because preoperative pressures were in the normal range and a deliberate effort was made to make the wrap 'floppy'.

Fundoplication is a successful operation for the control of gastro-oesophageal reflux but side-effects related to intestinal gas are common. The present study provides an explanation for this phenomenon. The nature of the relationship between the clinical outcome in an individual patient and the motility of the gastro-oesophageal junction awaits further study.

Acknowledgements

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Delay in treatment for oesophageal cancer

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Background Dysphagia is the cardinal symptom of oesophageal cancer, yet many patients present late. This study examined prospectively the interval between onset of dysphagia and treatment and identified reasons for delay.

Methods Patients with histologically confirmed oesophageal carcinoma were questioned about duration of symptoms and about each step of their diagnostic work-up. Delay was estimated from date of onset of symptoms to definitive treatment.

Results Median delay was 15 weeks for 78 patients with dysphagia, and 17 weeks for 22 patients with other symptoms. The most frequent cause of delay was late presentation to the family doctor (44 per cent). For patients treated with surgery alone there was a trend towards more advanced stage of disease with longer delay to treatment, but no correlation with survival ($P = 0{\cdot}25$).

Conclusion Lack of awareness of the sinister significance of dysphagia is the most important cause for delay in presentation of patients with oesophageal cancer.

The incidence of oesophageal carcinoma, particularly adenocarcinoma, is increasing[1,2]. Dysphagia is the most common presenting symptom, and recent onset of dysphagia for solids in patients of middle age or older should alert the clinician to the need for urgent investigation. Although dysphagia is classically held to be a late symptom indicating advanced disease, this may simply reflect the delay between onset of dysphagia and treatment. The aim of this study was to assess prospectively the time interval between the onset of dysphagia, or other symptoms, and definitive treatment in patients with oesophageal cancer referred to a specialist unit, and to identify the reasons for delay.

Patients and methods

Patients

One hundred and five consecutive patients with a histologically-confirmed diagnosis of oesophageal carcinoma were interviewed on admission to the surgical unit using a standard questionnaire. Patients were specifically asked when symptoms began and when they first attended the general practitioner, and were questioned about each step of the subsequent diagnostic work-up. Delay in treatment was estimated in weeks from the date of onset of symptoms as recalled by the patient, to the date of definitive treatment. Treatment consisted of either oesophagectomy, chemotherapy and radiotherapy followed by surgery as part of a prospective randomized trial[3], or palliative intubation. Where possible the patient's recollection of events was confirmed by correlation with the hospital records and with referral letters. An interval of 3 months or more between onset of symptoms and treatment was arbitrarily defined as an unacceptable delay in management.

Statistical analysis

Differences between groups of patients were assessed using Wilcoxon's rank sum test for comparing two independent groups followed by analysis of variance for comparison of three or more independent groups.

Results

Patients

One hundred and five patients with oesophageal carcinoma were studied prospectively. Five patients were unable to give a consistent history and were excluded. There were 70 men; the median age was 69 (range 37–83) years. Forty patients had squamous carcinoma, 57 adenocarcinoma and three patients had other tumour types (one each of basaloid, anaplastic and small cell carcinoma). Seventy-eight patients presented with dysphagia and 22 with other symptoms (*Table 1*). All but one patient presented to the family doctor. Sixty-five patients had been referred to a local hospital for investigation and subsequently transferred to this surgical unit. Four patients from the Dublin area had been referred by the family doctor to the medical gastroenterology service and one to the ear, nose and throat service at this hospital, and were then transferred to the surgical unit.

Because this is a national referral unit, direct referral of patients with dysphagia from family doctors is possible, but only six of these patients had been referred directly to the surgical outpatients department. Most patients from outside the catchment area of the hospital were referred

Table 1 Presenting symptoms

Presenting symptom	No. of patients
Dysphagia	78
Epigastric pain	6
Heartburn	3
Weight loss only	3
Odynophagia	2
Vomiting/regurgitation	2
Fatigue	2
Gastrointestinal bleeding	1
Nausea	1
Indigestion	1
Sore throat	1
Total	100

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by the consultant physician or surgeon at the patient's local hospital, where the initial investigations were carried out.

Patients presenting with dysphagia

For the patients who presented with dysphagia, the median time from onset of dysphagia to definitive treatment was 15 (range 4–52) weeks (*Fig. 1*). Only 26 patients (33 per cent) were treated within 13 weeks of the onset of dysphagia. All of these patients had consulted their family doctor within 6 weeks of the onset of symptoms, and were referred to the local hospital for investigation or referred directly to this hospital. The diagnosis of oesophageal cancer was made within 2 weeks by oesophagogastroduodenoscopy or barium swallow, and the patients were transferred promptly for further evaluation and treatment.

Fifty-two patients (67 per cent) with dysphagia waited 13 weeks or more from the onset of dysphagia to treatment. The most common cause of delay in treatment among these patients was delay in presentation to the family doctor, which occurred in 23 patients (44 per cent) (*Fig. 2*). Of these, 13 had never considered cancer as a possible cause of their symptoms. Delayed referral by the family doctor was the cause for delay in 14 patients (27 per cent). None of these was referred for appropriate investigations on first presentation, but had to make two or more visits, or consult another doctor before investigation was initiated. In the remaining 15 patients (29 per cent), hospital services were responsible for the delay in treatment. In two patients this resulted from initial misdiagnosis. Five patients were delayed by a long wait for appointments for either oesophagogastroduodenoscopy (DGD), barium swallow or outpatient clinics. This tended to be due to a combination of short delays such as waiting 1 month for an initial outpatient appointment, a further month for a radiography appointment and a further 2 weeks for a return outpatient visit to discuss the results. One patient experienced a significant delay in referral from one hospital service to another. For the 52 patients who experienced a delay of 3 months or more, the median delay due to hospital services of 4 (range 3–9) months was not significantly different from that attributable to the patient (5 (range 3–12) months), or to the family doctor (5 (range 3–10) months).

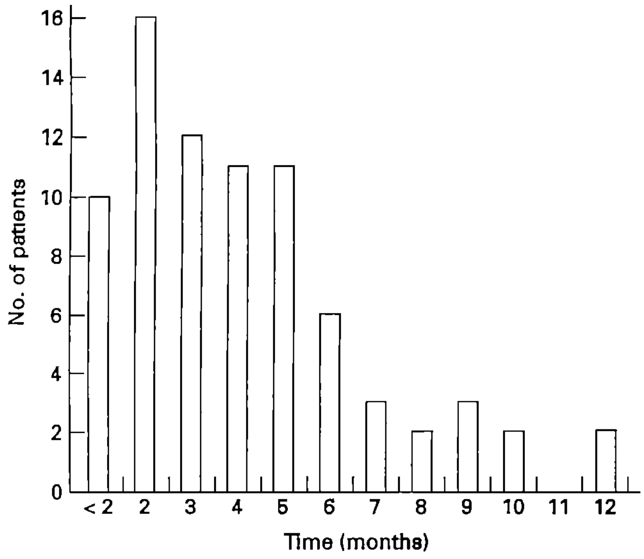

Fig. 1 Delay from onset of dysphagia to treatment

Patients presenting with other symptoms

Twenty-two patients presented with symptoms other than dysphagia. Symptoms included pain, heartburn, odynophagia, nausea, vomiting, haematemesis, sore throat and non-specific symptoms such as weight loss and fatigue. The median interval to treatment was 17 (range 0–30) weeks. Fourteen patients had a delay of 13 weeks or more before treatment. They presented a mean of 4·5 weeks after the onset of symptoms, but 13 were initially treated only with medication and were not referred for investigation. There was no correlation between tumour type and presenting symptom.

Acid-reducing medication

Fifty-two patients (52 per cent) were prescribed H_2 blockers (cimetidine or ranitidine) or omeprazole by the general practitioner as an initial measure, 18 of whom reported that the symptoms had been alleviated. In 20 (26 per cent) of the 78 patients who presented with dysphagia of recent onset, initial management consisted of a prescription for antiulcer medication without further investigation. Of 22 patients who presented with other symptoms 13 were treated initially with medication. Four patients had taken Gaviscon (Reckitt and Colman) or antacid of their own volition, only one of whom found it relieved the dysphagia.

Stage of disease

Fourteen patients were considered unfit for oesophagectomy because of age, pre-existing medical conditions, or presence of metastatic disease. The other 86 patients were randomized to either oesophagectomy alone or to combined chemoradiotherapy followed by surgery as part of an ongoing clinical trial[3]. As chemoradiotherapy may result in downstaging of tumours, reliable histological staging is available only for patients who were treated by surgery alone. Disease stage for patients who presented with dysphagia or other symptoms and were treated with surgery alone is shown in *Table 2*. A trend was identified between delay in treatment and stage of disease but the correlation was not significant

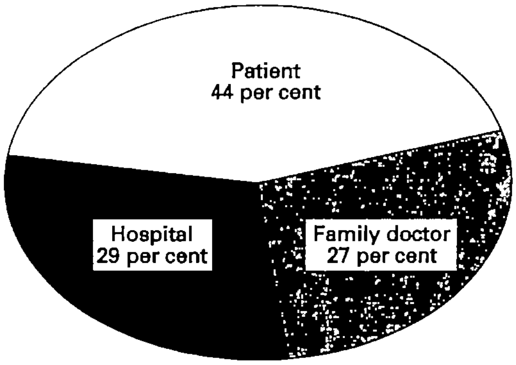

Fig. 2 Reasons for delay in treatment

Table 2 Histological stage of disease and length of delay in treatment of patients who had oesophagectomy alone

Stage	n	Median delay (weeks)	No of patients	
			Delay < 3 months	Delay > 3 months
Dysphagia				
Early (I–IIa)	10	16	4 (40)	6 (60)
Advanced (IIb–IV)	31	17	12 (39)	19 (61)
Other symptoms				
Early (I–IIa)	5	15	3 (60)	2 (40)
Advanced (IIb–IV)	6	17	0 (0)	6 (100)

Values in parentheses are percentages

($r = 0{\cdot}024$). There was no correlation between duration of symptoms and survival ($P = 0{\cdot}25$).

Treatment

Fifty-two patients were treated with surgery alone, 43 of whom were surgical controls in a randomized trial of neoadjuvant chemoradiotherapy *versus* surgery alone[3]. Thirty-four had neoadjuvant chemoradiotherapy followed by surgery, two had palliative chemotherapy, 11 had intubation and one patient with advanced disease received palliative care.

Discussion

What is an 'acceptable' time interval between onset of symptoms and treatment for patients with cancer? Ideally this should be minimal, but realistically there will always be a time lag between onset of symptoms and consultation with the family doctor, followed by a further interval awaiting assessment and management at a specialist clinic. For certain forms of cancer this time lag is short owing to increased public awareness. Women are becoming increasingly aware of the possible sinister significance of a breast lump and have rapid access to specialist clinics. For other forms of cancer with a lower public awareness and less specific symptoms, such as colon cancer, presentation is correspondingly delayed[4]. Oesophageal cancer is increasing in incidence[1,2] and presents with the very specific symptom of dysphagia, yet presentation is often late and treatment delayed. Three months was chosen as an arbitrary cut off as it should be possible, in an efficient health service, for the patient to appreciate that a problem exists and for a family doctor to arrange referral for appropriate diagnostic tests within this time frame.

This study suggests that the delay in treatment of patients with oesophageal cancer is due to a combination of delayed presentation by the patient because of lack of awareness of the disease, and delay in treatment resulting from inefficient management by both family doctors and hospital services.

In the 78 patients who presented with dysphagia, 67 per cent of patients waited 3 months or more for treatment and 20 patients (26 per cent) waited 6 months or more. This must be considered an unacceptable delay. Delayed presentation by the patient was the most important cause for delay in those patients who waited 3 months or more for treatment. Many patients treated the symptoms by self-medication for some time before consulting the family doctor. Most of these patients did not realize the sinister significance of their symptoms. This is probably the most difficult aspect of the problem to address, but suggests that public awareness of oesophageal cancer could be improved.

Two-thirds of patients who presented to the family doctor with dysphagia were referred promptly for endoscopy or barium studies, or to an appropriate referral service. One-third of patients, however, were not referred for investigation until the second or third consultation, or were referred for inappropriate investigation such as chest radiography or to a unit where oesophageal surgery was not performed. Several of these investigations needed to be repeated, including endoscopy and barium studies.

Dysphagia for solids is a relatively specific and sinister symptom, which warrants urgent investigation. The practice of prescribing antiulcer medication and advising the patient to return only if the symptoms persist is to be deprecated as it will inevitably lead to delay in diagnosis of some cases of oesophageal cancer. In this study symptoms of oesophageal cancer were alleviated by H_2 receptor blockers or proton pump inhibitors in 35 per cent of patients in whom they were prescribed, so improvement in symptoms should not be a contraindication to referral. In a separate study the authors have shown that patients with oesophageal cancer have impaired oesophageal motility[5]. This may predispose to reflux so it is understandable that prokinetic agents or proton pump inhibitors will alleviate symptoms in some patients at an early stage.

Hospital services were responsible for 29 per cent of the delays of 3 months or longer. As each outpatient visit entailed a 3–4-week wait for appointments and often significantly longer for outpatient radiography, the cumulative delay was often significant. A 'fast track' service is essential for such patients if earlier diagnosis is to be achieved. Open access gastroscopy is controversial. For patients with dysphagia, referral to open access endoscopy would avoid only those delays incurred while awaiting outpatient appointments, that is 23 per cent of cases in this study. Open access endoscopy tends to result in increased numbers of endoscopies, which may exacerbate delay by overloading the system[6]. A more selective approach would be to encourage family doctors to refer all patients over 40 years of age who present with dysphagia for early endoscopy. A programme in Birmingham aimed at early detection of gastric cancer reported encouraging results, and resulted in an increased proportion of potentially curative resections for gastric cancer[7].

It is difficult to prove from a hospital-based study that earlier diagnosis results in improved outcome for patients with oesophageal cancer, as referral pattern bias may result in an increased number of 'difficult' advanced cases. There was a non-significant trend towards a correlation between symptom duration and stage, and no link with increased survival. It is possible that lack of correlation with survival reflects the poor outcome for oesophageal cancer overall and the advanced stage of tumour in the majority of these patients. In this unit, 80 per cent of adenocarcinomas and 50 per cent of squamous tumours have lymph node involvement. Sixty-six per cent of patients undergoing surgery in this series had advanced disease with lymph node involvement.

In the Hunan province of China, where there is a very high incidence of the disease, screening for oesophageal cancer by annual endoscopy has resulted in a 5-year survival rate of 90 per cent for patients diagnosed by screening[8]. In a comprehensive review, Muller *et al.*[9] found that tumour stage at operation was the primary determinant of outcome in oesophageal cancer. Lymph node involvement significantly reduced the 5-year survival rate. One study of the rate of growth of oesophageal cancer[10] found that the average time for tumour size (as estimated from barium swallow examinations) to double was 6·4 months. Furthermore, there appeared to be an initial slow growth phase when tumour spread was confined to the mucosa and submucosa, followed by a faster growth phase when tumour spread from the submucosa to the adventitia. Diagnosis and treatment of oesophageal cancer in this early growth phase may result in improved survival.

Although a trend was observed between delay in presentation and more advanced stage of disease it did not reach significance and there was no correlation between delay and survival. A reduction in the interval between onset of dysphagia and treatment may result in a higher proportion of cancers being treated at an early stage. To achieve this the three main causes of delay in treatment must be addressed. First, public awareness of oesophageal cancer must be improved, and patients encouraged to seek medical advice at an early stage; second, family doctors should be aware of the necessity for urgent investigation of patients presenting with dysphagia, and should have rapid access to specialist referral centres; and, finally, specialist units must recognize the potential for significant delay for patients awaiting appointments for diagnostic services and should take steps to expedite this process. At the very least, patients with cancer deserve the opportunity to be diagnosed and treated at a stage of their disease when the likelihood of cure is greatest.

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Short note

Button caecostomy in the management of faecal incontinence

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Faecal incontinence is a physically disabling and psychologically distressing problem in some children with congenital disorders like spina bifida, anorectal malformation and Hirschsprung's disease. Various management protocols are frequently successful[1,2]. Malone *et al.* in 1990[3] introduced the antegrade continent enema to keep these children clean[4]; however, the Malone procedure may have problems[5].

A modification of the Malone procedure using a Corpak (Wheeling, Illinois, USA) button or Mic-key (Medical Innovations, Draper, Utah, USA) gastrostomy device is described.

Materials and methods

Between May 1994 and June 1995 seven patients underwent 'button' caecostomy after intensive efforts to make them acceptably continent had failed. There were four boys aged 13–17 years with spina bifida, a boy and a girl aged 10 and 7 years with Hirschsprung's disease and one boy of 8 years with an anorectal anomaly.

Every effort was made to explain all details of the procedure to the parents and children. All patients had enemas in the hospital for 2 days before the operation. Prophylactic antibiotic (Augmentin) treatment was commenced at induction of anaesthesia and continued for 5–7 days after operation. A suitable site (comfortably accessible for the parent and child) was chosen in the right iliac fossa. The caecum was exposed through a Lanz incision in the right iliac fossa sited a few centimetres below the proposed caecostomy site. Mobilization of the caecum was necessary in some cases to avoid tension on the stoma. In the first two patients a tube caecostomy was performed and this was then changed to a button after 6 weeks. The last five patients had a button caecostomy at the outset. A 16- or 18-Fr device of the correct length was used.

Antegrade continent enemas were started from the seventh postoperative day using normal saline. The volume of fluid (saline or tap water with a pinch of salt) needed in each patient ranged from 300 to 600 ml. Most children empty the colon in 15–30 min after instillation; the whole procedure takes about 45 min. The procedure is repeated every 24–48 h to achieve 'social continence'. Patients who tend to absorb most of the enema fluid empty quickly if bisacodyl is added to the enema fluid.

Results

Seven patients had a button caecostomy. Three of the patients (with spina bifida) had a ventriculoperitoneal shunt *in situ*. One patient had had a Malone procedure but was unable to catheterize the appendix and this was converted to a button after the appendicostomy was taken down. One patient had no appendix, this having been removed for diagnosing a long-segment Hirschsprung's disease. All patients had an uneventful recovery. All patients perform the enema at home and are clean. Two of the older patients need up to 1 litre of fluid to keep clean. One patient developed excessive granulation tissue around the stoma which had to be curetted. In two patients the device slipped out of the caecum but was replaced without difficulty. The children are comfortable at school and some of them participate in sports. The presence of an external device does not seem to affect them significantly. The parents believe that the lifestyle of their children has improved greatly.

Discussion

Lack of faecal or urinary continence is a great disadvantage and many patients with such incontinence are depressed and become introverted. Dedicated medical and paramedical personnel can help in making them socially acceptable. Dietary modifications, laxatives, enemas and toilet regimens serve to keep most of them clean. Some patients need further intervention. The Malone procedure met with significant success; the button antegrade continent enema is simpler and quicker to perform and is especially useful where the appendix is unavailable (although other modifications of the antegrade continent enema have been used these are by no means simple).

The insertion of an irrigation set into the button for purposes of enema is straightforward and painless, and parents and children quickly become adept at it. Patient selection is important; parents and children must perceive soiling as a major problem. There must be adequate commitment from them to carry out the enema diligently and a stable family environment is necessary to deal with problems.

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Short note

One-wound laparoscopic cholecystectomy

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Laparoscopic cholecystectomy is usually performed via three or four ports[1-3]. To reduce the trauma of access and thus improve patient compliance, many attempts have been made to perform cholecystectomy with fewer ports[4,5]. Experience with a one-wound technique is presented.

Patients and methods

Between May and October 1995, 30 patients underwent one-wound laparoscopic cholecystectomy Two skin incisions were created in the upper part of the umbilicus, and two 10-mm trocars were inserted. A 10-mm 0° or 30° laparoscope and different operating instruments were used. A 30° laparoscope was used when vision with the 0° laparoscope was imperfect. The patient was placed in a reverse Trendelenburg position and rotated to the left

Three sutures on a straight needle were passed through the abdominal wall in the right upper quadrant, through the gallbladder wall and then out through the abdominal wall again to raise the gallbladder and expose Calot's triangle. The first suture was positioned at the top of the fundus, the others on the neck and infundibulum of the gallbladder (*Fig 1*). The cystic duct and artery were separately identified, isolated, clipped and transected.

In eight patients intraoperative cholangiography was performed. Pulling alternately the sutures placed on the infundibulum and neck of the gallbladder, it was possible to move the gallbladder and so facilitate dissection of the gallbladder fossa. At the end, the little bridge of skin between the two skin incisions was cut, thereby creating a single wound; the gallbladder was withdrawn and the incision sutured. A subcutaneous injection of 3 ml bupivacaine completed the intervention.

Results

No procedures were converted to open operation. There were no intraoperative complications. Mean operating time was 123 min. The mean number of analgesic administrations was 0·1. Mean postoperative stay in hospital was 1·8 days. There were no deaths, but one case of wound infection.

Discussion

Only one skin incision was used, two 10-mm ports being created from the same wound, and multiple sutures were placed to suspend the gallbladder. This technique seems to offer several advantages: it needs only one skin incision and only two trocars, a 10-mm laparoscope (0° or 30°) allows perfect vision and the gallbladder is easier to withdraw, even when its wall is very thick, by joining the two umbilical incisions at the end of the procedure. The injection of bupivacaine in the wound at the end of the procedure reduced pain in the early postoperative period, and it was also possible to reduce postoperative hospitalization.

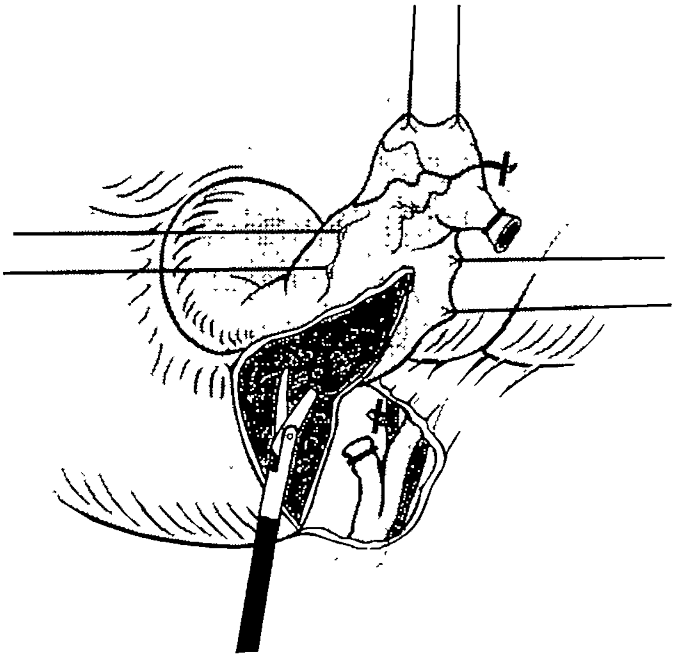

Fig. 1 Three sutures on a straight needle were passed through the abdominal wall, through the gallbladder wall and then out through the abdominal wall again to raise the gallbladder and expose Calot's triangle

Acknowledgements

Fig. 1 was drawn by Gillian Lee Illustrations.

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Surgical Research Society Abstracts

The following abstracts were presented at the 85th meeting of the Surgical Research Society. The meeting was organized by the Department of Surgery, King's College Hospital, and held on 2–3 January 1997 in King's College London. Ninety-seven papers were presented during the scientific sessions. The Patey Prize was awarded to Mr J. N. Lund for his paper entitled 'A randomized double-blind, placebo-controlled trial of glyceryl trinitrate in anal fissure'.

Anti-CD4 and anti-CD2 monoclonal antibodies synergize to induce tolerance to rat cardiac allografts

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CD4. a co-receptor in the T cell receptor (TCR) complex and CD2, a T cell co-stimulatory molecule, both play an important role in T cell activation. In this study the ability of monoclonal antibodies (Mabs) directed against these two molecules to induce transplant tolerance when used individually and in combination in a rat cardiac allograft model was examined.

In the low-responder rat strain combination (Lewis to DA) Mabs directed against CD4 (OX38) and CD2 (OX34) both induced long-term cardiac allograft survival when administered individually to graft recipients before operation (median survival time (MST) more than 100 days; $n = 8$ per group). Untreated control animals all rejected the graft promptly (MST 8 days). In the high-responder rat strain combination (DA to Lewis) neither anti-CD4 nor anti-CD2 Mabs led to long-term graft survival when used alone (anti-CD4 MST 18 days, $n = 5$; anti-CD2 MST 19 days, $n = 6$), with all animals ultimately rejecting the grafts. However, when the two Mabs were given in combination they had a synergistic effect on allograft survival (MST 49 days, $n = 17$) with eight of 17 recipients retaining the graft indefinitely (more than 150 days) When these animals were challenged with fresh cardiac allografts they showed donor-specific tolerance, accepting a second DA heart graft but rejecting a third-party PVG heart graft. These results suggest that Mabs directed against the CD4 and CD2 cell surface molecules synergize to promote transplant tolerance in a rat transplant model in which tolerance is recognized to be difficult to induce.

Induction of heat shock protein 72 attenuates ischaemia–reperfusion-induced microvascular injury

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Leucocyte adhesion to endothelium and migration into interstitial tissue is a pivotal step in the pathogenesis of ischaemia–reperfusion injury. Exposure of cells to a subcritical stress, such as hyperthermia (thermotolerance), may protect cells from subsequent injury, possibly by inducing 72-kD heat shock protein (HSP72) expression *in vitro*. However, the effect of thermotolerance on leucocyte–endothelial interaction *in vivo* is unclear. The objective of this study was to investigate the effect of thermotolerance on leucocyte adherence and migration caused by ischaemia–reperfusion injury in rat mesenteric postcapillary venules (28–32 μm) Sprague–Dawley rats were randomized into sham ischaemia–reperfusion, ischaemia–reperfusion and thermotolerance + ischaemia–reperfusion groups. Thermotolerance was induced 8 h before ischaemia–reperfusion injury by raising core body temperature to 41 ± 0·5°C for 15 min. Ischaemia–reperfusion injury was established by occlusion of the superior mesenteric vascular pedicle for 10 min, followed by 60 min of reperfusion. The number of adherent (Na) and migrated (Nm) leucocytes, and their rolling velocity (Rv), were measured by intravital microscopy at baseline (−10 min), ischaemia (0 min), and 10, 30 and 60 min after reperfusion. Values at 60 min are shown in the *Table*. HSP72 expression in mesentery, intestine and lung was determined by Western immunoblotting.

	Sham ischaemia–reperfusion	Ischaemia–reperfusion	Thermotolerance +ischaemia–reperfusion
Na (per 100 μm)	4·3(1·2)*	40·0(3·8)	7·3(0·9)*
Nm (per field)	4·7(0·3)*	51·8(9·5)	12·7(3·8)*
Rv (μm s^{-1})	46·2(1·8)*	30·0(3·1)	46·6(1·7)*

Values are mean(s.e.m.) $*P < 0·05$ *versus* ischaemia–reperfusion. (Student's *t* test)

In this model, induction of ischaemia resulted in a 92–94 per cent reduction in blood flow. Ischaemia–reperfusion significantly increased the Na and Nm at 30 and 60 min, and decreased the Rv of leucocytes at 10, 30 and 60 min after reperfusion. Thermotolerance significantly reduced the increase in Na and Nm and the decrease in Rv elicited by ischaemia–reperfusion. Expression of HSP72 was induced in all tissues by thermotolerance. Thermotolerance attenuated ischaemia–reperfusion-induced leucocyte–endothelial interaction, possibly by increasing tissue expression of HSP72.

Route of feeding after major surgery: effect on gut barrier function and clinical outcome

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Early postoperative enteral nutrition (EN) is purported to be of greater benefit than bowel rest and parenteral nutrition (PN) In experimental models, EN maintains gut defences and decreases the risk of endotoxaemia and sepsis compared with PN but this has not been evaluated in humans. This thesis and potential mechanisms were studied in a randomized clinical trial of patients following major upper gastrointestinal surgery.

Thirty patients undergoing oesophageal, gastric or pancreatic resection for malignancy were randomized to receive either EN ($n = 15$) or PN ($n = 15$) from day 1 to day 7 after operation. All patients had a jejunostomy catheter inserted at surgery. Intestinal permeability was measured by the lactulose–mannitol assay. Permeability, and levels of C-reactive protein (CRP) and serum immunoglobulin (Ig) M antiendotoxin (EndoCAb) antibodies were determined before operation and on postoperative days 1 and 7. Thirty-day septic morbidity was monitored

There was no significant difference in the incidence of septic complications between the groups (EN 27 per cent *versus* PN 47 per cent; $P = 0{\cdot}1$). Median permeability, CRP and endotoxin levels were as follows:

	Lactulose : mannitol ratio			CRP (mg l^{-1})			IgM EndoCAb (MU ml^{-1})		
		Postop			Postop			Postop.	
	Preop.	Day 1	Day 7	Preop.	Day 1	Day 7	Preop.	Day 1	Day 7
EN	0·05	0·14*	0·05	12	124*	92	170	128*	255*
PN	0·04	0·15*	0·06	8	135*	119	188	109*	250*

*$P < 0{\cdot}05$ *versus* preoperative (Wilcoxon signed rank test)

It is concluded that major surgical trauma increases intestinal permeability, in association with a heightened acute-phase response and evidence of endotoxin exposure. However, EN did not modulate further changes in these parameters compared with PN, nor did it reduce septic complications. The study failed to demonstrate a clinical or scientific basis to support the thesis that early postoperative enteral feeding reduces sepsis and preserves gut barrier function compared with gut rest and total PN.

Randomized trial of megestrol acetate alone *versus* megestrol acetate plus ibuprofen in patients with advanced pancreatic cancer

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Trials of the appetite stimulant megestrol acetate have demonstrated that a proportion of patients experience improved appetite and a proportion gain weight. Patients with pancreatic cancer cachexia frequently have an increased acute-phase response and an increased resting energy expenditure. Short-term administration of ibuprofen to patients with pancreatic cancer results in reduction of resting energy expenditure and the acute-phase protein response. The purpose of the present study was to investigate whether ibuprofen confers any additional benefit over treatment with megestrol acetate alone.

Forty-six patients with advanced pancreatic cancer (nine stage III and 37 stage IV) were randomized to receive megestrol acetate 480 mg day^{-1} and either ibuprofen 1200 mg day^{-1} or an identical placebo. Ethical permission was granted for the study, informed consent was obtained from all subjects, and both patients and observers were blinded to treatments. Patients were assessed before treatment and at 4, 8 and 12 weeks following treatment. Weight, arm anthropometry and serum C-reactive protein (CRP) levels were documented.

A high attrition rate was observed with only eight patients in each group attending for follow-up at 12 weeks. Median survival was 9 weeks for patients randomized to ibuprofen and 8 weeks for those given placebo (P not significant). In patients completing the 12-week treatment period, those receiving ibuprofen and megestrol acetate had a significant weight gain and improvement in arm anthropometry compared with those receiving placebo and megestrol acetate. The reduction in serum CRP level observed in patients receiving megestrol acetate and ibuprofen was not statistically significant compared with that observed in those randomized to megestrol acetate and placebo.

	Megestrol/ placebo ($n = 8$)	Megestrol/ ibuprofen ($n = 8$)	P*
Change in weight (kg)	−2·3(−3·0 to 0·5)	1·0(0 to 3·5)	<0·03
Change in arm muscle circumference (cm)	−1·5(−7·8 to 0)	1·2(−1·6 to 3·1)	<0·05
Change in triceps skinfold thickness (mm)	−1·5(−3·6 to −0·9)	0·6(−1·2 to 1·9)	<0·02
Change in CRP (mg l^{-1})	5(−8 to 32)	−13(−22 to 4)	n.s.

Values are median (range) at 12 weeks. *Mann–Whitney U test. n.s., Not significant

Nutritional indices improved in the ibuprofen–megestrol acetate group compared with continued decline in the placebo–megestrol acetate group. These results suggest that ibuprofen combined with megestrol acetate may offer improved nutritional benefit over treatment with megestrol acetate alone.

Multiple mechanosensors transduce the response of saphenous vein endothelium to arterial flow

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The adaptation to the arterial circulation of a new vein graft is crucial to its long-term patency. The differential responses of saphenous vein endothelial protein expression to longitudinal (shear stress) and circumferential deformation, and the potential for potassium channel blockade to abolish these responses, was investigated.

Saphenous vein segments, with or without an external polytetrafluorethylene stent to limit circumferential deformation, were perfused with oxygenated Krebs' solution in an *in vitro* bypass circuit (mean pressure 100 mmHg, 80 cpm, 15 dyne cm^{-2}) for up to 90 min. ICAM-1, VCAM-1, nitric oxide synthase (eNOS) and thrombomodulin (TM) were assessed by immunostaining (percentage of CD31 staining area) and Western blotting of endothelial cell lysates (ratio to vWF staining). Controls included freshly excised vein (basal), vein exposed to venous flow (90 min) and vein perfused with the potassium channel blocker tetraethylammonium chloride (TEA) 3 mmol l^{-1}.

No changes were observed after venous flow. Changes after exposure to arterial flow are shown in the *Table*.

	Basal (0 min)	Unstented (45 min)	Unstented (90 min)	Stented (90 min)	Unstented + TEA (90 min)
Immunostaining (percentage of CD31 staining area)	($n = 31$)	($n = 8$)	($n = 8$)	($n = 8$)	($n = 7$)
ICAM-1	21·4(1·4)	42·8(3·8)*	44·6(2·0)*	24·0(3·0)	20·0(1·0)
VCAM-1	16·6(3·4)	5·0(1·5)*	3·6(1·0)*	17·0(2·0)	17·5(2·0)
eNOS	52·1(5·6)	60·0(6·0)	70·1(5·0)*	73·7(5·0)*	47·0(3·0)
TM	68·4(6·0)	48·3(5·0)*	32·9(3·0)*	41·3(3·0)*	43·4(4·0)*
Western blotting (ratio to VWF staining)					
ICAM-1	0·2(0·0)	0·4(0·0)*	0·4(0·0)*	0·2(0·0)	0·2(0·0)
VCAM-1	0·4(0·0)	—	0·1(0·0)*	—	—
eNOS	0·3(0·0)	0·5(0·0)	1·5(0·1)*	0·6(0·1)*	0·2(0·0)
TM	1·4(0·3)	—	0·1(0·0)*	—	0·5(0·0)*

Values are mean(s.e.m.) *$P < 0{\cdot}05$ *versus* basal

The two-fold increase in ICAM-1 concentration on saphenous vein endothelium within 45 min of exposure to circumferential deformation was abrogated by potassium channel blockade. The upregulation of eNOS, 2–3-fold within 90 min of exposure to increased shear stress, was abrogated by potassium channel blockade. TM was downregulated within 45 min of exposure to raised shear stress even in the presence of potassium channel blockade. Saphenous vein endothelium appears to have at least two mechanosensors responsive to shear stress, one of which is coupled to potassium flux whilst a separate mechanosensor, coupled to potassium channels, responds to circumferential deformation.

Proton pump inhibitors in the treatment of bile-positive Barrett's oesophagus

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The aetiology of Barrett's oesophagus is not fully understood, although it is now accepted that the refluxate in this disease contains both alkaline duodenal juices in addition to acid. Some studies have suggested that proton pump inhibitors can control both acid and bile reflux. Seventeen patients with histologically proven Barrett's oesophagus were studied prospectively. All patients had station manometry performed followed by simultaneous bile and acid ambulatory 24-h monitoring. Bile-positive patients were then treated with omeprazole 20 mg daily for 4 weeks. Diet was unrestricted and bile data were analysed for interdigestive and supine periods.

	Pre-Rx	Post-Rx	P†
Mean(s.e.m.) acid score	90·7(4·2)	22·8(2·1)	<0·01
Interdigestive % bilirubin > 0·14 (absorbance units)*	56(10–77)	1(0–44)	<0·05
Supine acid (%)*	22(0–66)	0(0–60)	<0·05
Supine bilirubin (%)*	66(6–94)	5(0–93)	<0·05

*Values are median (range). †Wilcoxon rank sum test

Twelve of 13 patients with bile-positive reflux were also acid refluxers. However, after medical treatment four were still acid positive and five remained bile positive. One patient who was bile positive without acid responded to medical treatment. Four patients who were acid positive and bile negative had normal acid and bile exposure after treatment.

In conclusion, patients with Barrett's oesophagus have reflux profiles including acid alone, bile alone or both. Proton pump inhibitors are not consistently effective in controlling mixed refluxers at normal dosages. Ambulatory bile monitoring should be included with pH monitoring to clarify treatment options.

Changes in lymphocyte subpopulations during normal human wound healing

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The possible role of lymphocytes in normal human wound healing was evaluated by characterizing morphological changes in lymphocyte subpopulations at four defined stages of normal healing. A comparison was made with chronic wounds.

Serial 6-mm punch biopsies were taken from the edge of 12 normally healing pilonidal sinus excision sites at days 0, 7 and 21, and on day 42 if not healed. Single 6-mm biopsies were taken from ten patients with chronic venous leg ulcers. All tissue was snap frozen in liquid nitrogen and serial sections were stained with a panel of lymphocyte-specific monoclonal antibodies against CD45, CD20, CD19, CD3, CD4, CD8, CD25 and CD27. Numbers of lymphocytes and proportions of subpopulations were compared as healing progressed. Results are expressed as mean(s.e.m.) and statistical analysis was with Student's *t* test.

A higher CD4:CD8 (T helper:T suppressor) ratio of 4·0(0·5) was initially found in normally healing wounds compared with non-healing wounds (1·9(0·6); $P = 0{\cdot}02$). The ratio in normal wounds decreased as they healed ($P = 0{\cdot}04$ by day 21). Markers of proliferation of T lymphocytes, CD27 and CD25, rose from 26·2(4·0) per cent at day 0 to 46·9(6·0) per cent at day 42 ($P < 0{\cdot}01$), and from 9·4(1·0) per cent at day 0 to 17·9(3·5) per cent at day 42 ($P = 0{\cdot}04$) respectively. A significant rise in the number of CD8-positive cells, from 6·7(0·9) to 11·6(1·7) per field ($P = 0{\cdot}027$), and a decrease in CD4-positive cells from 22·6(3·2) to 16·2(2·5) per field ($P = 0{\cdot}13$) indicated that these proliferating cells were probably T suppressor lymphocytes. There was also a gradual rise in the proportion of CD19-positive B lymphocytes from 3·7(1·2) per cent ($P < 0{\cdot}02$ by day 7) to a level of 27·2(4·2) per cent by day 42 ($P < 0{\cdot}01$). Confirmation that these were B lymphocytes was obtained by staining for a separate antigen, CD20 ($r^2 = 0{\cdot}93$). This was in contrast to a low proportion of B lymphocytes (2·9(1·3) per cent) found in chronic wounds.

In conclusion, dynamic changes occur in the leucocyte subpopulations of normally healing human skin wounds and these are modulated as healing progresses. Differences exist between normal and abnormally healing wounds which indicate a potential role for lymphocytes in human wound healing. A rising T suppressor lymphocyte level as wounds heal and a high level in chronic wounds suggests that these cells play a part in downregulating the healing response in human tissue.

Protein truncation testing for *BRCA1* and *BRCA2* mutations: a possible screening test?

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Between 6 and 19 per cent of patients with breast cancer have one or more close relatives with the same disease. Breast cancer susceptibility genes have now been identified, *BRCA1* on chromosome 17q21·1 and *BRCA2* on chromosome 13q12. Mutations in these tumour suppressor genes are thought to account for 80 per cent of all familial cases of breast cancer, with mutation carriers having an 85 per cent lifetime risk of breast cancer. The *BRCA1* and *BRCA2* genes produce proteins that are believed to be members of the granin family of secreted proteins, and alteration to these protein products results in functional pathology. Both genes have over half their coding sequence contained within one exon, that is exon 11.

	GH (mu l^{-1})	Prolactin (mu l^{-1})	LH (units l^{-1})	Cholesterol (mmol l^{-1})
Pretreatment	1·1 (0·5–5·3)	230 (115–451)	35 (8–50)	5·9 (3·7–8·5)
After soy	2·9 (0·5–10·0)†	256 (66–681)†	31 (4–50)*	5·4 (3·7–7·3)†
After placebo	1·8 (0·5–7·8)	234 (83–641)	38 (12–50)	5·6 (4·2–6·9)

Values are median (range) *$P < 0{\cdot}006$, †$P < 0{\cdot}05$ (Mann–Whitney *U* test)

The authors have been screening the lymphocyte DNA of index cases from families with breast and ovarian cancer in Scotland for germline *BRCA1* and *BRCA2* mutations. These families have been identified as 'at risk' by the Department of Medical Genetics. Protein truncation testing (PTT) has been carried out on 150 patients. It is believed that alterations to the protein products of these genes results in functional pathology. PTT involves an initial non-radioactive polymerase chain reaction (PCR) followed by *in vitro* transcription and translation using a combined T7 rabbit reticulocyte lysate system. The resultant protein product is labelled with [^{35}S]methionine. After size separation by electrophoresis, the presence of any truncated products is observed by autoradiography. Any PCR products resulting in a truncated protein are then sequenced using an automated fluorescent sequencer.

Three different mutations have been identified in nine families. Five of these families show the same mutation, an AA deletion in exon 11 of *BRCA1* at position 2800 (AA2800). This results in an in-frame stop codon at nucleotide 2820. One individual was shown to be homozygous for this mutation, thereby giving rise to a naturally occurring human 'knockout' for this gene. This mutation appears to be common in the Scottish population. The other mutations were found in *BRCA2* at positions 5447 and 5574; these were a seven base-pair deletion and two base-pair deletion respectively, both resulting in truncated protein products.

These results demonstrate a rapid and efficient method of screening for germline mutations in patients with suspected familial breast cancer. Its use is recommended for predictive testing so that the patient, geneticist and surgeon may make informed decisions with regard to the case for prophylactic mastectomy.

Dietary soy supplementation is oestrogenic in postmenopausal women

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A high dietary intake of phyto-oestrogens is associated with prolongation of the menstrual cycle and a reduction in the incidence of breast cancer, believed to be due to an oestrogenic action of these plant oestrogens.

Postmenopausal women, aged 56 (range 43–65) years with severe vasomotor symptoms were given 60 g soy protein drink (80 mg total isoflavones), or placebo (casein), per day for 2 months, in a double-blind crossover trial to assess whether dietary supplementation with soy could reduce the frequency of hot flushes. Hot flushes were counted daily during the 6 months of the trial. Urine was collected to measure phyto-oestrogens (genistein, daidzein and equol) and serum for oestrogen, progesterone, luteinizing hormone (LH), follicle-stimulating hormone, prolactin, growth hormone (GH) and cholesterol. Levels of serum isoflavones were significantly higher during soy supplementation ($P < 0{\cdot}0001$).

Significant increases in GH and prolactin, and falls in LH and cholesterol were seen with soy supplementation but not placebo. Analysis of the frequency of hot flushes showed a reduction in patients on the soy diet ($P < 0{\cdot}03$). Soy phyto-oestrogens have oestrogenic properties in postmenopausal women and could potentially be used as treatment for hot flushes in women who have undergone cancer therapy.

Regulation of matrix metalloproteinases in colonic anastomotic healing

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Colonic anastomotic failure remains a serious problem in surgical practice. The mechanisms related to colonic healing are poorly understood. Matrix metalloproteinases (MMPs) are present at an anastomosis but not in normal colon. Little is known about their colonic regulation and the cells that synthesize the MMPs have not been identified. The cytokines interleukin (IL) 1β and basic fibroblast growth factor (bFGF), which are known stimulators of MMP synthesis, and transforming growth factor β (TGF-β), a downregulator of MMPs, were investigated.

A left-sided colonic anastomosis was performed in New Zealand White rabbits. These were killed at 6 h ($n = 6$) or 7 days ($n = 6$) and the anastomoses were resected. Immunofluorescence was used to visualize MMPs (MMP-1, MMP-2 and MMP-9) and tissue inhibitor of MMPs 1 (TIMP) simultaneously with the cytokines and cell markers.

MMPs and TIMP were present in the mucosa and submucosa of the cut edges of the bowel at 6 h; at 7 days they were restricted to the fibrin plug. The MMPs were synthesized by fibroblasts, except for MMP-9 which was seen in neutrophils. The cytokines were all upregulated at the anastomotic site but only IL-1β and TGF-β were at the same location as the MMPs. bFGF was increased in the muscle layer.

These results suggest that fibroblasts are the source of MMPs in colonic healing and that IL-1β and TGF-β may be involved in their regulation.

Gut permeability after limb ischaemia–reperfusion injury is not caused by systemic hypotension alone

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Limb ischaemia–reperfusion increases gut permeability, and hypotension or mediator release during reperfusion may cause this increase. The authors examined whether hypotension, without reperfusion, increased gut permeability to the level seen after limb ischaemia–reperfusion.

There were three groups of rats. One group had 5 h of bilateral hindlimb tourniquet ischaemia, the second 3 h of ischaemia and 2 h of reperfusion, and the third 3 h of ischaemia and 2 h of ischaemia plus haemorrhage to attain a fall in mean arterial pressure similar to that in the reperfusion group. Lactulose and mannitol were given through a jejunostomy tube 10 min before reperfusion or haemorrhage. At the end, blood was taken for measurement of portal oxygen extraction ratio, portosystemic difference in lactulose and mannitol concentration and aortoportal difference in standard bicarbonate.

	Control	Reperfusion	Haemorrhage
Bicarbonate (mmol l^{-1})*	1·1 (−0·3 to 2·5)	3·7 (2·8 to 4·5)‡	2·6 (1·1 to 3·6)‡
Oxygen extraction ratio	77 (71 to 83)	86 (83 to 89)‡	87 (84 to 91)‡
Lactulose (mg l^{-1})†	0·1 (0·1 to 3·1)	33 (12 to 51)‡§	4·0 (3·0 to 9·0)‡
Mannitol (mg l^{-1})†	2·0 (0·6 to 4·5)	32 (15 to 42)‡§	7·0 (5·0 to 8·0)‡

Values are *mean (95 per cent confidence interval) or †median (interquartile range), ‡$P < 0{\cdot}05$ *versus* control group, §$P < 0{\cdot}05$ *versus* haemorrhage group

Despite similar changes in mean arterial pressure and metabolic activities between the two experimental groups, gut permeability to lactulose and mannitol was significantly higher in the reperfusion group. This suggests that hypotension alone is not responsible for the increase in permeability seen after limb ischaemia–reperfusion injury.

Lymphokine-mediated downregulation of peripheral blood mononuclear cell cytokine release and acute-phase protein production in acute and chronic inflammatory disease models

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The T lymphokine interleukin (IL) 4 can downregulate IL-6 and tumour necrosis factor (TNF) production by peripheral blood mononuclear cells (PBMCs) from healthy volunteers. Production of such cytokines by PBMCs is thought to be an important event mediating the acute-phase protein response in acute and chronic disease. Attenuation of the acute-phase protein response may be a method whereby tissue catabolism could be reduced in wasting associated with inflammation. This study investigated whether IL-4 downregulates proinflammatory cytokine production by PBMCs from patients in an acute (multiple organ failure (MOF)) and chronic (cancer) model of the acute-phase protein response and if this is associated with a reduced ability to induce the acute-phase protein response *in vitro*.

PBMCs were isolated from controls, patients with gastrointestinal malignancy (chronic disease model) and patients with MOF (acute disease model). Cells were cultured in the presence and absence of lipopolysaccharide (LPS) 10 μg ml^{-1} with and without a 2-h preincubation with IL-4 10 ng ml^{-1}. IL-6 and TNF were measured in supernatants by enzyme-linked immunosorbent assay (ELISA). PBMC supernatants were then added to isolated human hepatocytes and their effect on production of the acute-phase protein alpha 1-acid glycoprotein was measured by ELISA.

IL-4 significantly downregulated release of TNF and IL-6 by LPS-stimulated PBMCs. Overall, preincubation of PBMCs with IL-4 resulted in downregulation of acute-phase protein production although variations were evident between groups (data not shown).

	IL-6 (ng ml^{-1})		TNF (pg ml^{-1})		Acid glycoprotein (ng ml^{-1})	
	No IL-4	IL-4	No IL-4	IL-4	No IL-4	IL-4
Control	7·4(0·7)	3·3(2·1)*	1675(296)	912(257)*	458(47)	364(49)*
Cancer	8·0(0·6)	2·6(0·7)*	1337(387)	394(198)*	672(57)	531(58)*
MOF	6·4(4·4)	1·6(3·1)*	1520(1091)	1053(926)*	635(80)	443(44)*

Values are mean(s.d.). *$P<0·05$ (two-tailed paired Student's *t* test)

These results demonstrate that cytokine production by PBMCs from patients with acute or chronic disease remains sensitive to downregulation by IL-4 and that this leads to attenuation of the potential of their supernatants to elicit an acute-phase protein response by human hepatocytes *in vitro*.

Endoluminal brushing: a simple, safe and effective technique for the *in situ* diagnosis of catheter-related sepsis

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A novel endoluminal brush has been designed to diagnose catheter-related sepsis (CRS) without the need for catheter removal. The brush is a sterile, closed system which is passed along the catheter to sample the lumen from hub to tip for bacteria After removal the brush tip is vortexed in 1 ml phosphate-buffered saline and aliquots are spread on to blood agar for quantitative culture. For comparison, following catheter removal catheter tips were cultured semiquantitatively by the Maki and modified Cleri methods to detect both external and internal bacterial colonization respectively. Experience with this technique in 245 patients, with central venous catheters of mixed types being used primarily for total parenteral nutrition, is reported.

	Brush	Maki	Cleri	Total
CRS	26	22	18	27
Catheter colonization	32	73	37	79
Negative	187	150	190	139

CRS, defined as significant catheter colonization (brush more than 100 colony-forming units (c.f.u.) per ml; Maki more than 15 c.f.u. ml^{-1}; Cleri more than 100 c.f.u. ml^{-1}) and positive peripheral blood cultures (taken before brushing) with the same organism, occurred in 26, 22 and 18 patients respectively. This gave sensitivities for brush, Maki and Cleri techniques of 96, 81 and 67 per cent, and specificities of 86, 69 and 87 per cent respectively. The Maki method is highly sensitive at detecting extraluminal catheter colonization, but appears too non-specific for the diagnosis of CRS.

It is concluded that the brush technique is both more sensitive and specific than conventional methods for the diagnosis of CRS, and does not rely on catheter sacrifice to confirm a clinical suspicion of such sepsis.

Liver metastasis thymidylate synthase level correlates with tumour response to floxuridine

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Treatment of colorectal liver metastases (CLM) with intrahepatic arterial floxuridine (FUDR) produces tumour response in only 50 per cent of patients. A test to predict responsive patients would rationalize management and reduce costs.

Thymidylate synthase is an enzyme involved in DNA biosynthesis and is the target for FUDR. The authors have examined whether estimation of intratumoral thymidylate synthase activity can predict which liver metastases respond to FUDR.

Liver metastasis biopsies were stained with an antithymidylate synthase antibody (TS106, courtesy of Dr P. G. Johnston, NCI, Maryland, USA). These patients with CLM then received intrahepatic FUDR treatment with determination of response by comparing computed tomography scans at the start and after 4 months of treatment. The intensity of TS106 cytoplasmic staining in eight 175 μm × 245 μm fields was assessed by two 'blinded' observers as either low (staining absent or weak) or high (staining moderate or intense).

	No. of patients	TS106 staining intensity	
		Low	High
Responders	10	7	3
Non-responders	15	5	10

$P = 0·04$ (Fisher's exact test)

The intensity of thymidylate synthase staining in tumour biopsies was associated with tumour response to fluorinated pyrimidine chemotherapy. However, use of this as a predictive test would only identify 70 per cent of responders and exclude 67 per cent of non-responders. This suggests that other factors may also determine response.

In vivo quantitative analysis of tumour angiogenesis with dynamic contrast-enhanced magnetic resonance mammography

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Tumour angiogenesis is an independent prognostic factor for patients with breast cancer. In experimental models microvessel density (MVD) has been shown to correlate with gadolinium enhancement assessed by dynamic magnetic resonance (MR) scanning. This study was designed to investigate the ability of dynamic contrast-enhanced MR mammography to provide a quantitative analysis of breast tumour angiogenesis *in vivo*.

Tumours were stained with factor VIII antibody. An image analysis system was used to aid microvessel counting. Preoperative MR mammography was performed using a 1·5T scanner with a dynamic sequence: 5-mm slice, 25 images per slice with a temporal resolution of 12 s per image. An image slice of whole tumour was selected as the region of interest and enhancement (E) was analysed at its maximum (Emax) and as relative increases in signal at 1 (E1), 2 (E2), 3 (E3) and 4 (E4) min after contrast.

Forty patients of mean age 58 (range 27–78) years were selected. There were 29 invasive carcinomas of the ductal type, six lobular, three tubular, one medullary and one mucoid tumour. Mean tumour size was 20 (8–50) mm and 18 patients were node positive.

Overall there was a significant correlation ($r = 0{\cdot}47$, $P = 0{\cdot}002$) with mean vessel count and E1 which improved to 0·70 ($P = 0{\cdot}001$) when node-positive tumours were considered. Maximum correlation was achieved between Emax and MVD in node-positive tumours ($r = 0{\cdot}77$, $P < 0{\cdot}0005$).

Contrast-enhanced dynamic MR mammography is able to provide a preoperative, non-invasive, *in vivo* quantitative analysis of MVD in breast tumours. This has obvious implications for the preoperative selection of high-risk patients for neoadjuvant therapy.

Characteristics and activation status of the immune infiltrate in human breast cancer

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Recent animal studies have demonstrated that spontaneously occurring breast cancers can be eliminated using an interleukin (IL) 2 gene-transfected tumour cell vaccine. The success of this type of immunotherapy in humans is possible only with a functionally intact cell-mediated immune system. The characteristics of the immune infiltrate, and the expression of IL-2 receptor (IL-2R) and major histocompatibility (MHC) class II antigen, was assessed in 60 breast cancers using immunocytochemistry on frozen sections.

The counting of cells stained was on a scale of 0 (no cells stained) to 3 (maximal number of cells stained). Over 90 per cent of breast cancers examined had a tumour infiltrating lymphocyte (TIL) count of 2 or 3. None of the tumours had an IL-2R count of 3, and only 10 per cent had a count of 0. In the subgroup of tumours with a TIL count of 3 ($n = 23$), there was equal distribution of IL-2R expression between minimal (1) and moderate (2). IL-2R expression was significantly associated with lymph node status ($P = 0{\cdot}02$) and histological grade ($P = 0{\cdot}05$) (Mantel–Haenszel χ^2 test). MHC class II antigen was expressed in all tumours except one, the expression being moderate or maximal in 80 per cent of tumours.

The interaction of T helper cells with tumour antigen, and their subsequent activation as shown by the expression of IL-2R, occurs in a MHC class II-restricted manner. Evidence for the expression of both is essential in determining the success of cell-mediated cytotoxicity.

Analysis of expression of $p16^{CDKN2}$ in primary breast cancer

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The cyclin-dependent kinase inhibitor $p16^{CDKN2}$, D-type cyclins, cyclin-dependent kinases (CDK) and the retinoblastoma protein (pRB) together constitute a G1 regulatory pathway which is commonly targeted in carcinogenesis. Deletion and/or mutation of p16 is an uncommon event in breast cancer, but transcriptional silencing via CpG island hypermethylation has been proposed as an alternative mechanism by which this gene may be functionally inactivated in cancer.

To address this question, p16 expression was analysed in 46 primary breast cancers and tumour-matched normal tissues using reverse transcriptase–polymerase chain reaction (RT–PCR)/Southern blotting and immunocytochemistry. CpG methylation in the p16 gene was studied by a highly sensitive, previously described PCR-based method. By RT–PCR, expression of p16 RNA was readily detected in 31 of 46 tumours. Expression of p16 protein was detected correspondingly in all tumours positive for RNA expression, but p16 was not detected in infiltrating lymphocytes nor in histologically normal breast tissue. Analysis of tumour-matched, normal breast tissue revealed p16 expression (RNA/protein) in only eight of 48 cases. Hypermethylation of CpG sites within the p16 gene was observed in 13 of 15 tumours negative for RNA/protein, but was not reproducibly detected in normal breast tissue.

Since upregulated expression of p16 is a surrogate marker for functional inactivation of Rb, these data suggest that inactivation of the p16/CDK4/D-type cyclin/pRB pathway is a common event in sporadic breast cancer. Inactivation through transcriptional silencing of p16 probably occurs in about 25 per cent of tumours. Alternative mechanisms such as mutational inactivation of pRB itself and overexpression of cyclin D2 or CDK4 may account for inactivation of this pathway in a significant proportion of the remaining tumours.

Value of diagnostic imaging for axillary lymph nodes

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The single most important determinant of prognosis in early breast cancer is axillary node status. Clinical assessment of the axilla remains inaccurate. Surgical clearance is associated with a certain morbidity. Imaging of the axilla is limited by the resolution of the imaging modality. Recent studies have suggested that magnetic resonance imaging (MRI) may accurately assess the axilla in patients with breast cancer. Lymph nodes of less than 4 mm are outside the resolution of MRI. The aim of this study was to evaluate the relationship between lymph node size and the presence or absence of tumour within the node.

Nodal size was measured directly from sections of archival material. Nodes without an intact capsule were excluded. In a second study, the effects of formalin fixation on lymph node volume were evaluated in ten patients by measuring lymph node volume before and after fixation.

	Node-positive	Node-negative
No. of patients	33	28
No of nodes examined	159	642
Nodes with an intact capsule	104	450
Size <0·4 cm	40 (38)	270 (60)
Size >0·4 and <1·0 cm	52 (50)	155 (34)
Size >1·0 cm	12 (12)	25 (6)

Values in parentheses are percentages

Formalin fixation caused a mean increase in nodal volume of 28·4 per cent. Thirty-eight per cent of positive nodes were less than 0·4 cm in diameter and would not have been detected by MRI.

It is concluded that MRI is of little value in the quantitative assessment of axillary lymph node involvement in primary breast cancer. Assessment of axillary node status by surgical clearance of the axilla remains the only accurate method of determining prognosis in early breast cancer. Imaging modalities such as MRI remain inaccurate.

Breast aspiration cytology: can local anaesthetic be used and are green needles better than blue ones?

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Fine-needle aspiration cytology is an established component of the 'triple assessment' of breast lumps. There is no consensus over which needle, green (21 G) or blue (23 G), should be used for this procedure and whether it actually affects the results. Some women find it a very painful experience; the use of local anaesthetic and its effect on the diagnostic accuracy of fine-needle aspiration cytology has never been addressed.

Sensitivity and specificity have been evaluated on standard surgical pathology specimens, comparing needle size and whether local anaesthetic interferes with the interpretation of the smears. Fifty-nine consecutive excised breast tumours (51 malignant, eight benign) were the targets for an 'on bench' study. A sample was taken with each needle and repeated after infiltration of 1 per cent lignocaine around the lesion. The order in which the needles were used was randomized. Standard aspiration technique was used with wet-fixed, air-dried and cytospin preparations. The smears were read blind independently by two cytopathologists.

There was excellent agreement for the cytodiagnosis between the different size needles with and without local anaesthetic (Kappa = 0·72–0·85). There were no false-positive results.

	No local anaesthetic (%)		With local anaesthetic (%)	
	Green	Blue	Green	Blue
Absolute sensitivity	84	84	82	84
Complete sensitivity	88	88	92	92
Positive predictive value	100	100	100	100
Negative predictive value	54	54	50	50

None of the differences was significant

This study shows, perhaps for the first time, that green and blue needles are equal in terms of their diagnostic accuracy and that the use of local anaesthetic does not result in the sacrifice of diagnostic information.

Effects of soy supplementation on epithelial proliferation in the normal human breast

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A high dietary intake of soy (i.e. in Japan and Singapore) has been associated with a reduction in the incidence of breast cancer in premenopausal women. Phyto-oestrogens present in soy inhibit human breast cancer cell proliferation *in vitro* and breast cancer development in animal models but no data exist for their effects on the normal human breast.

The aim of this study was to examine the effect of dietary soy supplementation on the proliferation rate of premenopausal normal breast epithelium. Twenty-nine women with benign or malignant breast disease were randomized either to placebo or 60 g soy supplement (containing 45 mg isoflavones) taken daily over 14 days. Biopsies of normal breast were labelled with $[^3H]$thymidine to detect the number of cells in S phase and immunocytochemically stained for the proliferation antigen, Ki67. The phyto-oestrogens genistein, daidzein, equol, enterolactone and enterodiol were measured in serum and urine samples obtained from women before and after supplementation.

Levels of isoflavones genistein and daidzein increased significantly ($P < 0{\cdot}01$) in the soy group at 14 days. There was a strong correlation between the Ki67 and thymidine labelling index ($r = 0{\cdot}949$, $P < 0{\cdot}001$). A significant increase in the proliferation rate of breast lobular epithelium after 14 days of soy supplementation was demonstrated when both day of cycle and age of patient were taken into consideration ($P < 0{\cdot}01$).

Short-term dietary soy stimulates breast proliferation (perhaps acting as an oestrogen agonist) and further studies are required to determine the effect of long-term supplementation on the pituitary gland and breast.

Doxycycline inhibits elastin degradation and metalloproteinase production in a model of aneurysmal disease

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Abdominal aortic aneurysms are characterized by degradation of the extracellular matrix with a reduction in the elastin concentration of the arterial media. These changes are mediated by increased levels of matrix metalloproteinases (MMPs) within the aorta, which provide a potential therapeutic target for pharmacological agents aimed at reducing the growth rate of small aneurysms. In this study, the ability of doxycycline to inhibit matrix degradation was assessed in a previously described *in vitro* model of aneurysmal disease.

Porcine aortic segments ($n = 7$) were preincubated in exogenous pancreatic elastase for 24 h before culture in standard conditions for 13 days with doxycycline 1 and 10 mg l^{-1}. Control segments were cultured both without doxycycline and without elastase. At the termination of culture MMPs and their inhibitors were extracted from the tissue and quantified by a combination of substrate gel enzymography and immunoblotting. The volume fractions of elastin and collagen were determined by stereological analysis of sections stained with Miller's elastin and Van Gieson stain.

	Elastin (%)	Collagen (%)	MMP-9 (units)
Control aorta	56·2 (46·9–64·6)	10·5 (9·2–13·9)	1·16 (0·87–1·43)
Elastase exposed	0 (0–4·2)*	81·5 (53·7–84·3)	1·55 (1·02–4·18)*
Elastase + doxycycline (10 mg l^{-1})	21·9 (14·8–31·0)*	42·6 (34·5–64·8)	0·88 (0–2·44)*

Values are median (interquartile range) $^*P < 0{\cdot}01$. Immunoblotting for tissue inhibitor of metalloproteinases (TIMP) 1 and TIMP-2 demonstrated equivalent production in all groups

Therapeutic ranges of doxycycline significantly inhibited elastin degradation and MMP-9 induction within the aortic organ cultures. These data suggest that doxycycline may have potential application in reducing the growth rates of small abdominal aortic aneurysms and clinical trials are suggested.

Myocardial injury in thoracoabdominal aortic aneurysm surgery

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Thoracoabdominal aneurysm (TAA) surgery is associated with considerable haemodynamic and ischaemia–reperfusion stresses especially at times of aortic clamping and unclamping. To assess the effect of these changes on the myocardium, plasma from 22 patients undergoing TAA surgery was collected at incision, supracoeliac cross-clamping, on reperfusion, and 1, 8, and 24 h thereafter. Samples were assayed for total antioxidant status (TPAS), the oxidative enzyme myeloperoxidase (MPO), lipid hydroperoxides (LHPs) as well as the myocardial-specific protein troponin-T. Data are presented as median (interquartile range) and statistical analysis was performed using the Wilcoxon signed rank test

Of the 22 patients, five developed intraoperative or postoperative electrocardiographic abnormalities and there was one cardiac death. There was a significant depletion of TPAS when the clamp was applied, on reperfusion and 1 h after reperfusion (all $P < 0{\cdot}001$). Levels of LHPs were significantly raised at the same time points with a maximum peak at reperfusion ($P = 0{\cdot}0001$). MPO levels showed a significant progressive increase from 24·5 (17·5–43·8) ng ml^{-1} at incision to 315 (35–770) ng ml^{-1} at 24 h ($P < 0{\cdot}001$ all points) Median troponin-T level at incision was 0·01 (0·01–0·02) ng ml^{-1}, and showed no significant increase on application of the clamp, on reperfusion and 1 h after reperfusion; however, at 8 and 24 h after reperfusion values reached 0·05(0·02–0·07) ng ml^{-1} ($P = 0{\cdot}0006$) and 0 02 (0·01–0·06) ng ml^{-1} ($P = 0{\cdot}005$) respectively. In the case of cardiac death, levels were 0·9 ng ml^{-1} at 1 h and 2·4 ng ml^{-1} at 8 h after reperfusion. There was a significant correlation between peak troponin-T level and TPAS ($r = -0{\cdot}5$, $P = 0{\cdot}0005$).

These data suggest the presence of significant subclinical remote cardiac injury in association with significant oxidative stress in TAA surgery.

Apparent heparin resistance in fibroblast-contaminated smooth muscle cell culture

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Vascular smooth muscle cell (VSMC) proliferation is important in the development of vein graft stenosis. Heparin has an antiproliferative effect which is specific for VSMCs. Resistance to heparin in cell culture has been reported in VSMCs derived from patients developing graft stenoses.

VSMCs were grown in culture from saphenous vein of patients undergoing infrainguinal ($n = 4$) and coronary artery ($n = 7$) bypass grafting. Cells were characterized by staining with antismooth muscle α-actin (anti-SMA) and antihuman fibroblast surface protein (anti-HFSP) antibodies. Growth curves were obtained and proliferation was assessed by incorporation of [^{3}H]thymidine in response to RPMI plus 15 per cent fetal calf serum with or without heparin 100 μg ml^{-1}

The increases in uptake of [^{3}H]thymidine by control samples varied markedly (median 3·7 (range 1·6–22·9)-fold). Median growth inhibition of VSMCs by heparin was 69 (range 53–93) per cent. One cell line which appeared to be heparin resistant (inhibition 19 per cent) stained with both anti-SMA and anti-HFSP antibodies, suggesting fibroblast contamination.

These early results have failed to confirm the existence of heparin resistance. Fibroblast contamination can produce similar findings. It is important to exclude positively the presence of fibroblasts with appropriate antibody before characterizing VSMCs as heparin resistant.

Hypoxia–reoxygenation-induced neutrophil adhesion to human skeletal myocytes

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Neutrophils (PMNs) are recruited into postischaemic skeletal muscle during reperfusion and are thought to promote subsequent muscle injury. However, it is not known whether this requires active PMN–myocyte adhesion and, if this is the case, how such an event is mediated.

In this study human skeletal myocytes (HSMs) were subjected to either 6 h of hypoxia (HX, 95 per cent nitrogen:5 per cent carbon dioxide) and 24 h of reoxygenation (RX; 95 per cent air:5 per cent carbon dioxide) or activation by tumour necrosis factor (TNF) α. PMN binding to HSMs was then assessed by incubating isolated PMNs (1–3 × 10^6 cells) with the HSMs for 15 min before the end of each experiment. Hypoxia alone increased PMN binding (non-adherent PMNs were removed by washing with phosphate-buffered saline) to HSMs compared with controls (mean(s.d.) 19·2(5 0) *versus* 4·6(1·7) PMNs per high-power field (h.p.f.); $P = 0{\cdot}005$) although there was no further increase following RX (17·0(3·9) PMNs per h.p.f.; $P = 0{\cdot}008$ *versus* control). By comparison maximal HSM activation with TNF-α resulted in the binding of 95·1(28·6) PMNs per h.p.f. ($P = 0{\cdot}007$ *versus* control).

Although TNF-α also upregulated ICAM-1 expression by HSMs after 6, 12, and 24 h of activation (mean(s.d.) 6·4(1·1)-fold, $P = 0{\cdot}004$; 8·5(2·2)-fold, $P = 0{\cdot}008$; 10·5(1·9)-fold, $P = 0{\cdot}002$ respectively) neither HX nor RX had such an effect. Furthermore neither anti-ICAM-1 nor anti-ICAM-3 antibodies reduced PMN adhesion after HX/RX. Conversely, both the absence of magnesium ions (required for integrin-mediated adhesion) and an anti-CD18 antibody reduced PMN binding (mean(s.d.) 0·6(0·4) PMNs per h.p.f., $P = 0{\cdot}003$; 0·7(0·3) PMNs per h.p.f., $P = 0{\cdot}004$ respectively).

These results are the first to demonstrate that PMN–HSM adhesion is an active process mediated by a CD18 integrin-dependent mechanism. This novel finding suggests that anti-CD18 antibodies may have a role in reducing PMN-mediated muscle injury following ischaemia–reperfusion.

Pharmacological reduction of endothelial swelling and leucocyte adhesion enhances blood flow and performance in ischaemic muscle

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Systemic neutrophil activation has been implicated in the progression of atherogenesis and is known to occur in claudicants during exercise.

The sodium ion–hydrogen ion antiporter blocker amiloride, the xanthine oxidase inhibitor allopurinol and indomethacin attenuate the capillary endothelial swelling and postcapillary venular leucocyte adhesion seen in ischaemic muscle. Using an established rat hindlimb model of intermittent claudication, the effects of each of the three drugs on blood flow and muscle performance have been compared in the tibialis anterior and extensor digitorum longus muscles. Exercising blood flow was measured using radioactive microspheres after 5 min of peroneal nerve stimulation. Isometric tensions were measured using strain gauges connected to a computer. Fatigue index was calculated as final tension/peak tension × 100. Results were analysed using analysis of variance and Fisher's PLSD post hoc tests

Mean(s.e.m.) blood flow after stimulation in control muscles was 96·1(19·7) ml per 100 mg per min ($n = 4$) and decreased to 0·4(0·1) ml per 100 mg after ligation ($n = 4$) ($P < 0{\cdot}0001$). Animals given allopurinol ($n = 4$) and indomethacin ($n = 5$) had a significantly higher blood flow (15·5(4·7) ml per 100 mg, $P = 0·02$ and 23·7(4·4) ml per 100 mg, $P = 0·006$ respectively). Flow in the amiloride-treated animals ($n = 6$) (8·9(3·2) ml per 100 mg) was not significantly different

Mean(s.e.m.) fatigue index in control muscles was 51·2(2·3) ($n = 4$) and decreased to 9·1(4·5) after ligation ($n = 8$) ($P < 0·0001$). Fatigue index was significantly greater in animals given allopurinol ($n = 8$) and indomethacin ($n = 8$) (28·2(5·8), $P = 0·02$ and 33·0(5·1), $P = 0·006$ respectively), but not in the amiloride-treated group ($n = 8$) (13·6(6·7))

The improvement in muscle blood flow seen in the treated groups is likely to be associated with a decrease in systemic neutrophil activation and a reduction in remote tissue damage. This may contribute to a reduction in the cardiovascular morbidity associated with intermittent claudication and is to be studied in human claudicants.

Transfection with a plasmid encoding a G-protein inhibitor reduces experimental vein graft intimal hyperplasia

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Vein grafts develop intimal hyperplasia due to smooth muscle cell (SMC) proliferation, with associated G-protein subtype changes. G-protein $\beta\gamma$ subunits stimulate cell proliferation through p21^{ras} pathways in response to certain mitogens. The $\beta\gamma$ subunits are also involved in activation of β-adrenergic receptor kinase 1 (βARK-1), the carboxyl terminus (βARK$_{CT}$) of which inhibits $\beta\gamma$ subunit activity *in vitro*. This study examined the effect of βARK$_{CT}$ on formation of vein graft intimal hyperplasia and G-protein function *in vivo*.

Forty New Zealand White rabbits underwent carotid interposition vein bypass grafting. Before grafting, veins were incubated in heparinized Ringer's lactate (controls; $n = 18$) or plasmid solutions containing either βARK$_{CT}$ ($n = 14$, 190 μg ml^{-1}) or empty plasmid DNA (plasmid· $n = 8$; 190 μg ml^{-1}) for 30 min at 37°C. Twenty-four vein grafts (ten controls, six plasmid and eight βARK$_{CT}$) were harvested at 28 days by perfusion fixation Intimal and medial dimensions of vein grafts were calculated and sections were taken for electron microscopy (EM). Ten vein grafts (five control and five βARK$_{CT}$) were analysed for *in vitro* contractile responses to noradrenaline (NA) and serotonin (5HT) in the presence and absence of pertussis toxin (PT) to categorize G-protein receptor coupling. Six vein grafts (three control and three βARK$_{CT}$) were harvested at 3 days for analysis of βARK-1 protein and messenger RNA (mRNA) expression.

At 3 days, βARK$_{CT}$ mRNA and protein were only expressed in the βARK$_{CT}$-treated vein grafts. At 28 days, there was a significant reduction in intimal thickness in βARK$_{CT}$-treated vein grafts compared with either plasmid or control vein graft intima without a change in medial thickness (*Table*). Transmission EM of βARK$_{CT}$ vein graft showed SMC remnants with apoptotic changes. Contractile studies demonstrated a loss of PT sensitivity to NA and 5HT in βARK$_{CT}$-treated vein grafts compared with control grafts (*Table*).

				Contractility studies			
Group	Intima (μm)	Media (μm)	I M ratio	NA	NA+PT	5HT	5HT+PT
Control	70(4)	65(5)	0·52(0·02)	6·00(0·09)	5·16(0·09)†	6·34(0·10)	5·54(0·26)†
Plasmid	70(4)	58(7)	0·54(0·02)	—	—	—	—
βARK$_{CT}$	45(4)*	76(3)	0·36(0·02)*	5·91(0·19)	5·81(0·18)*	6·57(0·10)	6·55(0·13)*

Values are mean(s.e.m.) I M Ratio = intimal area/intimal + medial areas Contractility is shown as $-\log \mathrm{ED}_{50}$ *$P < 0·01$ *versus* control, †$P < 0·01$ *versus* vessel not treated with PT (analysis of variance)

Transfection of vein grafts with βARK$_{CT}$ results in a 37 per cent reduction in intimal hyperplasia and alterations in G-protein receptor coupling (loss of PT sensitivity) This study demonstrates βARK$_{CT}$-mediated inhibition of $\beta\gamma$ function *in vivo* and suggests that targeting G-protein pathways may offer new strategies for reducing vein graft intimal hyperplasia and subsequent graft failure.

Successful gene transfer to vein grafts using a replication-deficient adenovirus

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Vein bypass grafting remains a major treatment for patients with occlusive arterial disease. Although bypass grafting improves both limb survival and patient symptoms, vein graft failure secondary to thrombosis and intimal hyperplasia limits success. Gene therapy approaches using adenovirus may have potential to limit vein graft failure. Successful adenoviral gene transfer to both normal and injured arteries has been demonstrated. Vein grafts are more accessible for intraoperative gene transfer than arteries; however, the effects of vein grafting on gene transfer efficiency are unknown The efficiency of adenoviral gene transfer to vein grafts was compared with that to native vessels.

Eight New Zealand White rabbits had a carotid bypass performed using reversed jugular vein, following adenoviral *in vivo* gene transfer of the marker gene, β-galactosidase (β-Gal). Contralateral jugular vein (JV) and carotid artery (CA) also underwent gene transfer. A viral titre of 1×10^9 plaque forming units per ml was delivered by luminal dwell for 30 min in each vessel. β-Gal expression was assessed by x-gal staining (cell nucleus stains blue) and by measurement of β-Gal protein in vessel extracts using an enzyme-linked immunosorbent assay. Thirty-two vessels from eight rabbits were studied for β-Gal expression 3 days after gene transfer, with untransfected aorta as controls. All gene-transferred vessels stained blue with x-gal, with virtually 100 per cent of endothelial cells (ECs) transduced. No blue cells were seen in uninfected aorta. Immunohistochemical analysis using anti-CD18 antibodies revealed marked leucocyte infiltration in the vein graft endothelium, but not native vessels, with an associated disruption of endothelial integrity

	CA	JV	Vein graft
β-Gal expression (ng per mm vessel length)	3·0(1·6)†	3·2(3·1)	1·4(0·9)
No. of β-Gal-positive ECs per section	197(57)*	182(57)‡	109(51)

Values are mean(s.e.m.). *$P < 0·01$, †$P < 0·03$, ‡$P < 0·05$ *versus* vein graft (analysis of variance)

Gene transfer to rabbit CA and JV is highly efficient and generates high levels of β-Gal expression. Despite intense endothelial injury, β-Gal levels in vein grafts remain approximately 50 per cent of that in control JV

Interleukin 12 as a target molecule for prolonging allograft survival

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Interleukin (IL) 12 is a key immunoregulatory cytokine which promotes TH 1 responses and heightens cell-mediated immunity (CMI). Allograft rejection is usually attributable to CMI. The purpose of this study was to determine whether *in vivo* administration of a neutralizing antibody to IL-12 has a beneficial effect on allograft survival in a mouse transplant model.

C57B16 mice were grafted with skin from semiallogeneic BD2F1 donors. Mice treated with neutralizing polyclonal anti-IL-12 antibody (0·5 mg intraperitoneally on days −1, 2, 5 and 8 after grafting) rejected skin grafts at the same time as unmodified recipients (median survival time (MST) 11 days for both groups) However, in mice pretreated with donor-specific splenocytes (5×10^7 intravenously at day −7) and anti-IL-12 antibody (0·5 mg on days −8, −5, −2 and 1) graft survival was significantly prolonged (MST 17 days *versus* 10 days in recipients given splenocytes alone; $P < 0{\cdot}002$).

Lymphocytes from treated animals were stimulated *in vitro* with irradiated donor splenocytes and supernatants were analysed by enzyme-linked immunosorbent assay. Cells from control animals produced high levels of TH 1 cytokines (interferon γ and IL-2) whereas cells from animals treated with donor splenocytes plus anti-IL-12 produced low levels of TH 1 cytokines but high levels of IL-10 and IL-5 (TH 2 cytokines)

These results suggest that neutralization of IL-12 together with administration of donor spleen cells reduces CMI and delays allograft rejection. IL-12 may be an important target molecule for therapeutic strategies in transplant rejection

Outcome following femoropopliteal angioplasty: importance of ankle:brachial pressure index

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This study assessed the clinical outcome and restenosis rate of patients undergoing femoropopliteal percutaneous transluminal angioplasty (PTA).

Over a 1-year period 67 consecutive patients (mean(s.d.) age 71(8) years, 39 per cent women; intermittent claudication 39, rest pain five, ulceration 20, gangrene three; median length of lesion 2 (range 0·5–15) cm) treated by femoropopliteal PTA were followed prospectively, with duplex scanning of the angioplasty site and clinical assessment (grading outcome as SVS −3 to +3) performed at 1 day, and 3, 6, 9 and 12 months. The reliability of duplex scanning in defining arterial restenosis was confirmed by comparison with angiography. Univariate comparisons (unpaired t test and χ^2 test), life-table analysis and backward stepwise regression were used to investigate clinical and plasma risk factors for restenosis.

In 64 patients angiography immediately following angioplasty showed no evidence of residual stenosis (50 per cent or more), whilst in three technical failure occurred. Duplex assessment at 24 h identified a velocity ratio of more than 2·5 at the angioplasty site in ten patients The ankle:brachial pressure index (ABPI) increased from a mean(s d.) of 0·6(0 1) before angioplasty to 0·9(0 1) at 24 h. Two occlusions occurred within 7 days, and by 6 months restenosis (velocity ratio more than 2 5) was identified in 21 patients (33 per cent), four (6 per cent) had died, two (3 per cent) had undergone operation and one repeat angioplasty At 6 months, 43 patients (64 per cent) had a good clinical outcome (SVS +3 or +2) while in 18 patients (27 per cent) there was minimal clinical improvement (SVS +1 or less) The only preangioplasty characteristic associated with a poor prognosis was a low ABPI ($P = 0{\cdot}03$); type of lesion ($P = 0{\cdot}6$), lesion length ($P = 0{\cdot}8$) and number of patent crural vessels ($P = 0{\cdot}2$) did not predict outcome After PTA, neither angiography nor duplex scanning (24 h) predicted outcome at 6 months ($P = 0\ 9$). However, ABPI at 24 h predicted both restenosis ($P = 0{\cdot}001$) and clinical outcome ($P < 0{\cdot}001$) at 6 months. Life-table analysis demonstrated that 58 per cent of patients with a 24-h ABPI of less than 0 9 compared with only 18 per cent of patients with a 24-h ABPI of 0·9 or more developed restenosis by 6 months ($P = 0{\cdot}04$). Triglyceride, cholesterol, smoking markers, sICAM-1 and fibrinogen did not influence outcome

In conclusion, restenosis occurs in one-third of patients within 6 months of femoropopliteal angioplasty. Success of PTA is difficult to predict but restoration of an ABPI of 0 9 or more suggests a satisfactory outcome.

Cellular origin and effects of proinflammatory cytokines in patients with oesophageal cancer

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The proinflammatory cytokines may mediate the paraneoplastic phenomena associated with cancer. The aim of this study was to examine the regulation of proinflammatory cytokine production in patients with oesophageal carcinoma.

A novel flow cytometric technique allowed the detection of intracellular cytokine in peripheral blood mononuclear cells from normal controls ($n = 18$) and patients with oesophageal cancer before treatment ($n = 30$), and also in tumour and normal epithelium ($n = 11$).

Intracellular tumour necrosis factor (TNF) α and interleukin (IL) 6 levels in T cells and peripheral blood monocytes from the patients with cancer were increased significantly ($P < 0{\cdot}05$) compared with those in cells from normal controls at 0, 24, 48 and 72 h in culture, with or without PMA stimulation. Slight increases were observed for IL-1β in monocytes. PMA-stimulated TNF-α levels are given in the *Table*.

	TNF-α (median fluorescent intensity)			
	0	24	48	72
T cells				
Cancer	30(3)	73(9)	100(11)	116(15)
Control	20(2)*	43(7)*	61(8)*	67(12)*
Monocytes				
Cancer	72(8)	177(27)	147(13)	150(18)
Control	40(3)*	113(16)*	109(10)*	108(18)

Values in parentheses are s.e.m. *$P < 0{\cdot}05$ (analysis of variance)

Changes in cytokine levels were confirmed by enzyme-linked immunosorbent assay. Plasma C-reactive protein and serum amyloid A levels were also raised in the patients with cancer. Increased levels of TNF-α and IL-6 were detected in tumour infiltrating monocytes and T cells compared with cells from normal mucosa. There was also an increased production of TNF-α and IL-6 in tumour epithelial cells compared with normal epithelium Maximal TNF-α and IL-6 levels were seen in those patients with cancer who had lost weight, compared with those whose weight remained stable.

This is the first report that conclusively demonstrates a global dysregulation of proinflammatory cytokine production in patients with solid gastrointestinal tumours. Cytokine responses appear to be associated with increased weight loss and acute-phase response. These cytokines may provide novel therapeutic targets to alleviate both patient morbidity and death.

Should senior surgeons and radiologists see the emergencies?

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The objective of this randomized controlled trial was to determine if abdominal ultrasonography and plain film radiography substantially enhances senior surgical assessment in reducing surgical admissions.

The trial included 95 emergency referrals (mean age 51 years, 37 per cent male) to general surgery in a teaching hospital, selected for intra-abdominal emergencies not requiring immediate surgery. The main outcome measure was number of patients not admitted.

Some 30 per cent of the intervention group and 10 per cent of the controls did not need admission (95 per cent confidence interval on this 20 per cent difference, 12–28 per cent). There were no important differences in the mean waiting time in casualty, length of admission, surgical intervention, readmission with similar pathology within 3 months or mortality rate within 3 months.

It is concluded that abdominal ultrasonography and plain film radiography enhances senior surgical assessment in reducing unnecessary surgical admissions.

Model for gene therapy for familial adenomatous polyposis: lipofection of the *APC* gene into mouse colon *in vivo*

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APC is a tumour suppressor gene which is premutated in the hereditary cancer syndrome familial adenomatous polyposis (FAP) and also shows somatic mutation in the majority of cases of sporadic colorectal cancer. The use of tumour suppressor genes to prevent carcinogenesis in at-risk tissues has been largely unexplored as an option for cancer gene therapy. The authors have previously reported to this society the lipofection of human *APC* gene into colonic epithelial cells *in vitro* with high levels of expression of the transgene for 3–4 days after treatment. The *in vivo* transfection of a normal copy of the human *APC* gene into mouse rectal epithelium is now reported.

Under the appropriate Home Office licence, 4-week-old male NIH/S mice were treated with an enema preparation of *APC* complementary DNA, contained in the *APC* pCMVβ-Neo Bam plasmid, complexed with the liposome LipofectAMINE in aqueous solution. Rectal tissue, liver and testes were harvested at intervals from 24 h after treatment and messenger RNA was extracted. Using reverse transcriptase–polymerase chain reaction for gene analysis, human and mouse sequences could be distinguished and expression of the human transgene detected.

The normal human *APC* gene was expressed by mouse rectal epithelial cells for up to 24 days after delivery of a 'liposome gene enema'. This is much longer than previously reported and exceeds the turnover time of rectal epithelium. These results suggest for the first time that stem cell gene transfer has been achieved by lipofection of the *APC* gene. There was no expression of the transfected gene at any time by liver or testes of treated animals.

This study has demonstrated that *APC* gene transfer is safe and efficient, and allows progression to a therapeutic trial of gene therapy with the human *APC* gene in the MIN (murine intestinal neoplasia) mouse, an appropriate model for FAP.

Randomized, double-blind, placebo-controlled trial of glyceryl trinitrate in anal fissure

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The standard treatment for anal fissure is internal anal sphincterotomy. There is concern over the effects of this procedure on continence. Nitric oxide donors such as glyceryl trinitrate (GTN) cause a reversible 'chemical sphincterotomy' capable of healing the fissure.

Eighty consecutive patients were randomized to receive treatment with topical 0·2 per cent GTN ointment or placebo in a double-blind study. Maximum anal resting pressure (MARP) was measured using a constantly perfused side hole catheter before and after the first application of trial ointment. Anodermal blood flow was measured throughout the manometry by laser Doppler flowmetry. Trial ointment (GTN or placebo) was applied to the anoderm twice daily by the patient. Healing and pain score were assessed at 2-weekly review. Hospital ethics committee approval was obtained.

After 8 weeks healing was observed in 26 of 38 patients treated with GTN but only three of 39 patients treated with placebo. Linear analogue pain score fell significantly in both groups after 2 weeks of treatment. This fall was maintained in those treated with GTN but pain scores returned to pretreatment values by 4 weeks from the start of treatment with placebo. Mean(s.d.) MARP fell significantly from 115·9(31·6) to 75·9(30·1) cmH$_2$O ($P < 0{\cdot}001$, Student's paired t test) in subjects treated with GTN but no change was seen in MARP after the application of placebo. Anodermal blood flow significantly increased after application of GTN but was unaffected by placebo.

Topical GTN provides rapid, sustained relief of pain in patients with anal fissure. Over two-thirds of patients treated in this way avoided surgery otherwise required for healing. This treatment may replace surgery as first line treatment for chronic anal fissure.

Oncolytic adenoviral therapy for p53(−) tumours

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Mutation of the *p53* tumour suppressor gene is the most common gene alteration in human cancers and is present in 50 per cent of all cancers. Therefore, *p53* is an ideal target for genetic therapy.

The authors' E1B deleted adenovirus, dl1520, selectively replicates in and lyses p53(−) cells. *In vitro* and *in vivo* studies show that this virus may have a therapeutic role in the treatment of p53(−) tumours.

Cytopathic effect assays were carried out on a range of p53(−) and (+) human cell lines. Cells were infected with dl1520 or with wild-type adenovirus Ad2 and monitored over the subsequent days for cytolysis. Wild-type adenovirus showed no selectivity and produced cytolysis in both p53(−) and p53(+) cell lines, dl1520 produced cytolysis only in the p53(−) cell lines.

In vivo studies were carried out using the C33A human cervical cancer cell line. Xenografts were produced in athymic mice by subcutaneous injection. The dl1520 virus at a dose of 10^8 or 10^9 plaque forming units was then injected directly into the tumour mass. After 6 weeks, partial regression to complete regression had occurred. These data show that dl1520 is highly oncolytic for p53(−) tumours *in vivo*.

Genetic therapy using dl1520 may be a novel treatment for p53(−) tumours. Possible uses include direct intratumoral injection of p53(−) soft tissue tumours, e.g. of the head and neck, and breast; stereotactic intratumoral injection of brain tumours; intrahepatic artery injection of liver metastases; and intraperitoneal injection for ovarian carcinomatosis.

Based on the *in vitro* and *in vivo* studies, the authors are carrying out a phase I clinical trial on the treatment of recurrent p53(−) tumours of the head and neck by direct intratumoral injection.

Gastrin may have an autocrine/paracrine role in Barrett's oesophagus and oesophageal adenocarcinoma

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In colorectal cancer the gastrin gene is activated and both precursor and mature gastrin peptides may mediate autocrine/paracrine growth pathways. The aim of the study was to determine gastrin gene activation and provide evidence for an autocrine growth pathway in oesophageal neoplasia.

Samples were taken from patients with oesophageal adenocarcinoma ($n = 10$), Barrett's oesophagus (all forms of metaplasia and degrees of dysplasia; $n = 5$ for each group) together with normal oesophagus ($n = 5$). Specimens were stained with polyclonal antisera against progastrin, glycine-extended gastrin, amidated gastrin and the gastrin/CCKB receptor. Binding of the primary antibody was detected using the avidin–biotin–peroxidase method. Samples were assessed blind for site and degree of staining Expression of the gastrin and gastrin/CCKB receptor genes was confirmed by use of the reverse transcriptase–polymerase chain reaction.

Immunocytochemistry demonstrated that progastrin, glycine-extended gastrin, amidated gastrin and the gastrin/CCKB receptor were expressed at high levels in all oesophageal adenocarcinoma samples and at a similar level in all the Barrett's samples, irrespective of metaplasia type or degree of dysplasia. Staining was cytoplasmic with polarization at the plasma membrane. No expression of any gastrin was seen in normal mucosa.

It is concluded that the gastrin autocrine/paracrine pathway is absent in normal oesophageal mucosa; however, its presence has been confirmed in oesophageal adenocarcinoma. The gastrin gene is activated at an early stage in the progression of Barrett's oesophagus.

Allelotype of adenocarcinoma occurring in Barrett's oesophagus

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Certain genetic mutations, including the loss of function of tumour suppressor genes, have been implicated in the development of malignant tumours. The loss of function of a tumour suppressor gene can be identified by loss of heterozygosity (LOH) studies; these were performed on 16 cases of adenocarcinoma occurring in patients with Barrett's oesophagus.

All autosomal chromosomal arms were studied, and eight of these arms demonstrated LOH in more than 40 per cent of the tumours: 3p, 5q, 9p, 11p, 13q, 17p, 17q and 18q.

These sites of LOH were refined using further microsatellite markers, which indicated that LOH on chromosomes 9p, 13q, 17p and 18q occurred at the sites of the *MTS1*, *Rb*, *p53* and *DCC* tumour suppressor genes respectively. Loss of these genes has also been implicated in various other tumours.

The refined areas on 3p, 5q, 11p and 17q are thus putative sites of novel tumour suppressor genes associated with the development of Barrett's adenocarcinoma. It is of note that 70 per cent of tumours displayed LOH at the 17q11·2–q12 locus, and it is proposed that this is the site of the main tumour suppressor gene involved in the development of adenocarcinoma in Barrett's oesophagus.

It is hoped that these tumour suppressor genes may prove useful as biomarkers of future carcinogenesis in patients participating in Barrett's surveillance programmes

Continuous early enteral feeding preserves intestinal permeability following gastro-oesophageal resection

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Septic complications are associated with significant morbidity and mortality rates in patients following resection of gastro-oesophageal carcinoma. Endotoxaemia and bacterial translocation secondary to increased intestinal permeability have been implicated in the pathogenesis of these septic complications Although controversial, enteral feeding (TEN) appears to be superior to parenteral nutrition (TPN) in minimizing the incidence of postoperative septic complications. The aim of this study was to assess the impact of the route of nutritional support (TPN *versus* TEN) on intestinal permeability.

Intestinal permeability was measured using a novel differential polyethylene glycol (PEG) absorption technique. Nineteen patients undergoing resection were studied, of whom 12 received TPN and seven TEN via a feeding jejunostomy. Bowel permeability was measured, PEG 3350 and PEG 400 being used as orally administered probes. Each patient had permeability measured before operation and 7 days after operation.

	Before operation		After operation	
	PEG 400 (%)	PEG 3350 (%)	PEG 400 (%)	PEG 3350 (%)
TPN ($n = 12$)	15·1 (9·5–19·7)	0·09 (0·07–0·14)	18·0 (12·2–28·3)	0·31 (0·22–0·41)*
TEN ($n = 7$)	18·6 (12·9–21·4)	0·13 (0·04–0·15)	11·0 (10·6–12·2)	0·02 (0·02–0·03)†

Values are median (interquartile range) percentage urine retrieval of PEG probe *$P < 0·01$ *versus* before operation, †$P < 0·01$ *versus* TPN group (Wilcoxon signed rank test and Mann–Whitney U test)

Before operation, there were no significant differences between the two groups in intestinal permeability. Seven days after operation, patients who received TPN had significantly increased intestinal permeability to PEG 3350 compared both with before operation ($P < 0·01$) and with those who received TEN ($P < 0·01$).

The findings suggest that enteral supplementation is important in the maintenance of intestinal mucosal integrity and help explain the lower incidence of septic complications in patients who receive enteral rather than parenteral nutritional support.

Interphase cytogenetics of non-dysplastic Barrett's oesophagus

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Barrett's oesophagus is the major risk factor for oesophageal adenocarcinoma. The progression to malignancy probably involves several genetic events Little, however, is known about the genetic events occurring in the metaplastic epithelium before dysplasia develops. The aim of this study was to identify chromosomal alterations, consistent with the potential for malignant progression, in non-dysplastic Barrett's mucosa.

Multiple endoscopic biopsies were taken from 14 patients with uncomplicated Barrett's oesophagus, including normal oesophagus and stomach as controls. The frozen biopsies were sectioned, clustered on slides and subjected to interphase cytogenetics. Fluorescent *in situ* hybridization was performed with centromere-specific probes to chromosomes 1, 8, 9, 12, 17 and 18. Signals per nucleus were counted for 200 cells per biopsy, using a confocal microscope and image analysis system. The chromosome index (CI) was calculated (no. of signals/no. of nuclei). The mean(s.d.) CI for controls was 1·63(0·12) and any value >3 standard deviations from the mean was regarded as abnormal.

Chromosome	No. of biopsies	No. of patients	Chromosomal changes
1	16	5	No abnormality
8	5	3	No abnormality
9	19	6	2 gains (Patients 3 and 5)
12	9	4	1 loss (Patient 2)
17	6	2	No abnormality
18	33	14	No abnormality
Total	88	14	3 alterations

Chromosomal changes occur in uncomplicated Barrett's oesophagus at a low frequency, consistent with the hypothesis that genetic alterations are rare in non-dysplastic disease. Clonal divergence, reflecting the histological heterogeneity of Barrett's mucosa, is suggested by the fact that changes do not occur at all biopsy sites in each patient.

Pilot study of the hepatic perfusion index as a staging tool in oesophagogastric tumours

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The hepatic perfusion index (HPI) is the ratio of hepatic arterial flow to overall liver blood flow. A rise in the index above 0·37 predicts overall mortality rate and occult liver metastases in colorectal cancer. This work assessed the staging of oesophagogastric tumours by HPI using dynamic hepatic scintigraphy. Seventy-two patients with oesophagogastric cancer were studied; data are currently available on 31 patients of median age 68 years (six squamous, 25 adenocarcinomas) at a median follow-up of 10 months.

Thirteen of 14 patients who died during the study had a raised HPI compared with seven of 17 survivors ($P<0·01$; sensitivity 0·93, specificity 0·58). Initial staging with computed tomography (all 31 patients) and laparoscopy (in 23) suggested that 12 were inoperable (of whom nine had raised and three normal HPI) and 19 were operable (11 raised, eight normal HPI) (P not significant; sensitivity 0·75, specificity 0·43). Sixteen curative procedures were undertaken on those considered to be operable. Three patients had surgical palliation only, all of whom had a raised HPI; 13 had curative resection, five with a raised and eight with a normal HPI ($P=0·06$; sensitivity 1·0, specificity 0·61). Of patients who had a curative procedure, eight of 11 survivors had a normal HPI and both of those who died had a raised HPI ($P=0·06$; sensitivity 1·0, specificity 0·72).

This pilot study suggests that the HPI is a powerful preoperative predictor of death in patients with oesophagogastric tumours and allows more appropriate patient selection for surgery. Further study is required to assess if HPI is independent of pathological staging in predicting outcome in those considered suitable for curative resection.

Omeprazole effectively reduces gastro-oesophageal bile reflux as well as acid reflux

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Omeprazole markedly reduces gastro-oesophageal acid reflux but its effect on bile reflux has not been well documented. Using a fibreoptic bilirubin probe, the effect of omeprazole on bile reflux can now be measured objectively on an ambulatory basis.

Ten patients (six women; mean age 52·8 (range 28–77) years) underwent manometry followed by combined 24-h dual-channel pH (oesophageal and gastric) and oesophageal bilirubin monitoring. All acid suppression had been stopped for 7 days. The oesophageal probes were placed 5 cm above the lower oesophageal sphincter (LOS) and the gastric pH probe 15 cm distal to this. Twenty-four-hour monitoring was repeated after 6–10 weeks of treatment with omeprazole 20 mg twice daily.

Mean LOS pressure was 3·9 mmHg. Six of ten patients had a non-specific motility disorder. All had good symptom relief on treatment. Before treatment there was acid reflux (pH less than 4) for median (interquartile range) 18·8 (10·0–22·4) per cent of the total time; alkaline reflux (pH greater than 7) for 13·6 (11·3–20·8) per cent of the total time; bile reflux (abs. more than 0·14) for 24·6 (9·0–46·6) per cent of the total time; and gastric alkaline shift (pH greater than 4) for 9·8 (2·7–15·0) per cent of the total time. With omeprazole these percentages were: acid reflux 1·0 (0·5–1·6) ($P<0·001$ *versus* pretreatment; Mann–Whitney U test); alkaline reflux 4·5 (0·4–9·6); bile reflux 2·3 (0·5–7·1) ($P<0·001$); and gastric alkaline shift 55·4 (44·7–70·0) ($P<0·001$). There was a significant decrease in oesophageal acid and bile reflux with omeprazole, a significant increase in gastric alkaline shift, and a non-significant fall in oesophageal alkaline time.

In view of the likely role bile plays in the pathogenesis of Barrett's oesophagus, these results are encouraging for those receiving medical treatment. The mechanism by which omeprazole produces this effect is the subject of further investigation.

Are changes in survival from oesophageal cancer related to changes in the incidence of histological subtypes?

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The incidence of oesophageal carcinoma in the Western world is known to be increasing, largely because of increases in adenocarcinoma, but trends in survival have received little attention.

Using data from the Merseyside and Cheshire Cancer Registry from 1974 to 1993, time trends in incidence and survival were examined, including analysis for both squamous cell carcinoma and adenocarcinoma histological subtypes.

Over the 20-year study period, the incidence of squamous cell carcinoma has remained relatively constant, whereas the incidence of adenocarcinoma has more than doubled. This increase in adenocarcinoma was seen in both sexes and all age groups. Significant improvements in the 1-year (from 15 to 24 per cent), 2-year (from 7 to 15 per cent) and 5-year (from 4 to 10 per cent) survival rates from oesophageal carcinoma were observed over the study period. There was no significant difference in survival from squamous cell carcinoma and adenocarcinoma, and the improvements in survival were almost identical for both histological subtypes. Improvements in the 2-year and 5-year survival rates were more substantial after 1988.

These results suggest that the observed changes in survival from oesophageal carcinoma are unlikely to be due to changes in the pattern of incidence of histological subtypes. Changes in the management of oesophageal carcinoma, particularly after 1988, should be explored as an alternative explanation for these changes.

Objective assessment of lower oesophageal sphincter dynamics after laparoscopic Nissen fundoplication

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Laparoscopic Nissen fundoplication (LNF) is an effective procedure for the treatment of gastro-oesophageal reflux disease (GORD), but its mechanism of action remains a subject of controversy. The purpose of this study was to evaluate the results of LNF, with particular emphasis on the lower oesophageal sphincter (LOS) pressure dynamics as assessed objectively by oesophageal manometry and 24-h pH monitoring.

Twenty patients with history of GORD underwent stationary oesophageal manometry (using Konigsberg solid-state catheter and Synectics polygram software for computerized analysis) and 24-h pH monitoring, both before and 3 months after LNF. All manometry tracings were reviewed blindly in a random fashion. The parameters analysed included: LOS resting and residual pressure, LOS length, number of reflux episodes and percentage of the time at pH below 4 during upright and supine positions.

	Before LNF	After LNF	P*
LOS resting pressure	26 (12–88)	34 (16–55)	<0·05
LOS residual pressure	3 (0–14)	9 (0–16)	<0·01
LOS length	3 (2–5)	4 (2–6)	<0·05
% time pH<4 (upright)	10 (0–40)	0 (0–7)	<0·001
% time pH<4 (supine)	6 (0–35)	0 (0–6)	<0·01
No of reflux episodes	48 (2–107)	3 (0–12)	<0·01

Values are median (interquartile range). *Wilcoxon rank test

LNF eliminated reflux in all patients. One of the mechanisms underlying the antireflux action of LNF is the increase in mean LOS residual pressure at the gastro-oesophageal junction during swallow-induced LOS relaxation. This may be a purely mechanical effect extrinsic to the LOS caused by the fundic wrap.

Oesophageal acid exposure after cholecystectomy is due to cholecystokinin-mediated transient lower oesophageal sphincter relaxation

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There is a significant increase in gastro-oesophageal reflux after cholecystectomy which is unrelated to reduced lower oesophageal sphincter pressure Transient lower oesophageal sphincter relaxations (TLOSRs) are a possible mechanism by which this effect might occur. The authors have previously demonstrated that cholecystokinin is increased postprandially in these patients after surgery. Cholecystokinin has been implicated in TLOSRs. The aim of this study was to examine whether postprandial acid exposure is raised after cholecystectomy

All patients had station oesophageal manometry followed by 24-h oesophageal pH studies with the probe placed 5 cm above the upper border of the lower oesophageal sphincter. Analysis of pH results for the postprandial period (1 h following each meal) in 27 patients was carried out before cholecystectomy and 3 months after operation. Twenty patients with rheumatoid arthritis were used as controls.

	Postprandial acid exposure (%)
Cholecystectomy group	
Before cholecystectomy	5 (0–20)†
After cholecystectomy	9 (0–27)
Control group	4 (0–20)*

Values are median (range). *$P<0{\cdot}02$, †$P<0{\cdot}04$ *versus* after cholecystectomy (Wilcoxon rank sum test)

After cholecystectomy patients had significantly higher postprandial acid exposure than controls and before operation. Patients who were symptomatic for reflux following cholecystectomy had higher postprandial acid scores than those who were asymptomatic.

It is concluded that gastro-oesophageal reflux after cholecystectomy is predominantly postprandial. TLOSRs due to raised cholecystokinin level may mediate this effect

Does duplex graft surveillance improve limb salvage?

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Graft-related stenosis following femoropopliteal/distal (FPD) vein bypass can frequently be detected within 30 days when intervention can maintain patency and improve limb salvage. Subsequent surveillance utilizes limited resources and may be of less benefit.

Some 109 FPD vein bypasses were performed between October 1993 and March 1996. Sixty-five (group 1) were referred for duplex surveillance after 1, 3, 6 and 9 months, and at 1 year, 31 (group 2) were followed up clinically. Thirteen patients suffered graft failure, amputation or died within 30 days and have been excluded from further analysis.

In group 1, 18 grafts (28 per cent) developed stenoses Ten were revised, of which four restenosed and occluded. By comparison, three of the eight untreated grafts occluded ($P=0{\cdot}37$, Fisher's exact test). In group 2, four symptomatic grafts were successfully revised. The *Table* shows comparative cumulative life-table results at 1 year.

	Group 1	Group 2	P*
Primary patency (%)	71	64	>0·2
Assisted primary patency (%)	87	76	>0 1
Limb salvage (%)	98	96	>0 2
Survival (%)	91	87	>0·2

*Log rank test

In patients whose grafts remain functional beyond the first month, duplex surveillance has little effect on graft patency, limb salvage or patient survival. A randomized clinical trial is required to demonstrate a significant benefit before continuing with its use routinely in clinical practice.

Effect of anaesthetic technique on cerebral oxygenation during carotid surgery

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Carotid cross-clamping (CXC) during carotid endarterectomy performed under local anaesthetic (LA) results in a rise in mean systemic blood pressure which improves cerebral oxygenation (autoregulation). However, surgery under LA may have a greater risk of cardiac complications and have limited appeal to both surgeon and patient. It has been suggested, however, that the intravenous general anaesthetic (GA) agent propofol also preserves cerebral autoregulation and so changes in systemic blood pressure and cerebral autoregulation (near infrared spectroscopy (NIRS–HbO_2)) have been assessed in patients undergoing carotid endarterectomy under LA ($n=10$), a propofol-based GA ($n=10$) or a conventional volatile inhalational-based GA (isoflurane, $n=10$).

Mean(s.d.) blood pressure before cross-clamping was 126(9) mmHg, 97(3) mmHg and 99(2) mmHg respectively (LA *versus* GA groups: $P<0{\cdot}01$). Following CXC mean blood pressure rose in all patients under LA (145(7·9) mmHg; $P<0{\cdot}01$), but did not alter in the propofol (99(3·4) mmHg) or isoflurane (100(2) mmHg) groups. Cerebral HbO_2 saturation (NIRS) fell in nine of ten patients who had LA, all of those given propofol and in nine of ten who had isoflurane. This recovered spontaneously in seven of nine, one of ten, and one of nine patients respectively (LA *versus* GA groups: $P<0{\cdot}05$). Similarly a shunt was required in only two of ten patients who had LA (awake testing) compared with seven of ten given propofol (mean stump pressure less than 50 mmHg, $P<0{\cdot}05$) and five of ten anaesthetized with isoflurane (P not significant).

These results indicate that compared with LA a propofol-based GA does not preserve cerebral oxygenation during carotid endarterectomy and confers no benefit over a conventional GA. LA would thus appear to be the anaesthetic technique of choice, at least in terms of neuroprotection, for carotid endarterectomy.

Is quality of life influenced by varicose vein surgery?

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Varicose vein surgery primarily aims to improve the quality, and not the duration, of patients' lives. This study assessed the impact of (1) varicose veins and (2) varicose vein surgery on patients' quality of life.

Two groups of patients were studied prospectively. Group A consisted of 35 patients (11 men, 24 women) aged 16–82 (median 49) years who completed Short Form 36 (SF36) and EuroQol (EQ) instruments, before (A1) and 6 months after (A2) surgery for varicose veins. Control group B consisted of 33 patients (seven men, 26 women) aed 25–73 (median 47) years who had previously completed quality of life questionnaires (B1) and were selected from the 6-month duplex scan waiting list to complete further questionnaires (B2).

Initial SF36 scores (A1 + B1) demonstrated significantly increased pain and limited physical functioning when compared with age- and sex-matched scores ($P<0{\cdot}01$, Mann–Whitney U test). Questionnaires A1vB1 and A1vA2 revealed no significant differences in any of the quality of life domains. Questionnaires B1vB2 revealed significant deterioration in the SF36 measured physical role, pain ($P<0{\cdot}01$), physical functioning and general health ($P<0{\cdot}05$) (Wilcoxon matched pairs test). Questionnaires A2vB2 revealed significant improvement in the EQ measured pain and general health ($P<0{\cdot}05$, Mann–Whitney U test) with surgery.

Varicose veins sufferers report significantly more quality of life limitations than a matched population. Quality of life deteriorates whilst patients are waiting for scans and surgery stops this deterioration. This study supports continued provision of venous surgery as a health care service and input of resources to keep waiting lists below 6 months.

Objective mobility recording in the assessment of peripheral vascular disease

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An objective measurement of mobility in the home environment is needed to fully assess treatment outcomes for leg ischaemia which is not limb threatening This study reports on mobility monitoring of such patients and controls using the NUMACT recorder.

Twenty patients (median age 65·5 (95 per cent confidence interval (c.i.) 60·5–70·5) years) with claudication ($n=18$) or rest pain ($n=2$) (median ankle:brachial pressure index 0·6 (95 per cent c.i. 0·5–0·6)) and 13 normal subjects with no disabling medical condition (median age 68 (95 per cent c.i. 63–72·5) years) were studied. Each subject wore a NUMACT recorder for 24 h at home. This is a modified Psion computer with two position sensors and an accelerometer. Posture (standing, sitting, lying) and activity (steps and amplitude of steps) were recorded in real time for 24-h periods.

	Lying (min)	Sitting (min)	Standing (min)	No of steps	Energy
Patients	768	476	186	7 088	172 761
($n=20$)	(667–862)	(365–570)	(143–231)	(5 587–9 372)	(112 548–262 294)
Controls	644	428	371	14 216	472 505
($n=13$)	(574–706)	(346–499)	(316–433)	(11 742–17 942)	(338 361–759 522)
P*	0·06	0·48	<0·01	<0·01	<0·01

Values are median (95 per cent c.i.) *Mann–Whitney U test

These data demonstrate reduced standing time, half as many steps and one-third the energy expenditure in patients with peripheral vascular disease compared with age-matched controls.

NUMACT provides comprehensive objective mobility recording at home. This should be used when comparing different treatment regimens for non-critical leg ischaemia.

Abnormalities of the haemodynamic response to exercise in claudicants

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The aim of this study was to identify abnormalities of the haemodynamic response to exercise in claudicants.

A purpose-built ergometer allows a supine, unilateral, 5-W, 5-min duration, square-wave, plantar–flexion exercise test. Special design features ensure that the thigh remains still, so that continuous common femoral artery blood flow measurements can be made using an Ultramark 9 colour duplex machine, with High Q automatic analysis, and 5-MHz transducer. Graphs of blood flow *versus* time are produced.

Graphs were obtained from 32 normal and 119 stable calf claudicant limbs. Semilogarithmic plots showed that the normal haemodynamic response to exercise can be approximated to a monoexponential function of time. Claudicants showed three response types: single-phase monoexponential (44 per cent), two-phase monoexponential (24 per cent), and no form (32 per cent). The response magnitude was reduced in claudicants ($P=0{\cdot}00$, Mann–Whitney test) but the response speed was faster ($P=0{\cdot}00$).

As the haemodynamic response to exercise includes rapid cardiogenic and slower vasodilatory components, the increased response speed of claudicants suggests that in these patients, the cardiodynamic component predominates. The two-phase response of some claudicants may represent abnormal vasodilatation when metabolites exceed a threshold level.

This study demonstrates abnormalities of the form, speed and magnitude of the haemodynamic response to exercise in claudicants. These findings have implications for the development of new treatment strategies; for example, is the abnormal vasodilatory response the reason for the inefficacy of vasodilator therapy?

Do blood pressure changes affect cerebral oxygenation during carotid endarterectomy?

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Although it is suggested that maintenance of a high systemic blood pressure (BP) during carotid endarterectomy (CE) improves cerebral oxygenation, this has not been examined critically. This study assessed the effect of alterations in mean BP on middle cerebral artery velocity (MCAV) (transcranial Doppler ultrasonography), jugular venous oxygen saturation (SJvO$_2$, a measure of cerebral oxygen extraction) and cerebral oxygenated haemoglobin levels (HbO$_2$, near infrared spectroscopy) during CE.

Some 24 patients who demonstrated changes in mean systemic BP greater than 10 mmHg lasting for more than 1 min during the carotid cross-clamp period were investigated. Of these, 17 had a rise in BP, six a fall, and one an initial rise followed by a fall.

A rise in mean(s.d.) systemic BP from 97(3·5) to 116(4·7) mmHg ($P<0{\cdot}001$) was associated with an increase in MCAV from 42(4·5) to 46(4·8) cm s^{-1} (P not significant). Simultaneously there was a small but non-significant rise in both SJvO$_2$ (from 71(1·9) to 74(1·9) per cent) and cerebral HbO$_2$ (+2(0·1) μmol dl^{-1}) levels. Conversely when mean(s.d.) systemic BP fell from 132(10·6) to 100(9·1) mmHg ($P<0{\cdot}01$), mean

MCAV also fell (from 58(7·3) to 46(7·8) cm s^{-1}, $P<0\cdot05$). This was associated with a reduction in both $SJvO_2$ (from 74(2·6) to 70(1·9) per cent) and HbO_2 levels ($-$ 1(0·08) μmol dl^{-1}. These falls were not significant.

Although there was a significant correlation between the changes in BP and MCAV ($r=0\cdot63$, $P<0\cdot01$), there was no correlation between either of these parameters and $SJvO_2$ or HbO_2 level.

Thus, although MCAV is dependent on mean systemic BP, changes in these indices do not directly influence measures of cerebral oxygenation in normotensive patients. Thus there is no evidence to support the concept of artificially manipulating BP during CE.

Correlation of abdominal aortic aneurysm wall compliance with current predictors of rupture risk

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Assessment of the risk:benefit ratio of surgical repair of abdominal aortic aneurysm (AAA) is currently made on the basis of diameter, expansion rate and patient fitness. However, for the individual patient, these measurements alone may not reliably predict the risk of rupture. AAA wall behaviour such as compliance, as measured by the pressure–strain elastic modulus (Ep) and stiffness (B), may provide a more accurate risk stratification.

The purpose of the study was to describe the relationships between maximum AAA diameter, rate of expansion and compliance.

Diameter, Ep and B were measured with the Diamove echo-tracking system (Teltec, Sweden) interfaced with an EUB 240 ultrasound scanner (Hitachi, Japan) using a 3·5-mHz transducer. A 486 personal computer showed aortic diameter change during the cardiac cycle over 11 s. Growth rate per month was calculated from 6-monthly follow-up scans over 1–4 years for 60 of 94 consecutive subjects with AAA.

Satisfactory results were obtained in 88 per cent of patients Growth rate (median 0·16 (range 0·0–0·56) mm per month) showed a significant positive correlation ($r^2=0\cdot56$, $P=0\cdot00$) with maximum diameter (median 46·4 (range 29·6–79·2) mm). Poor correlation ($r^2=0\cdot16$, $P=0\cdot08$) was found between maximum diameter and elasticity (median 2·39 (range 0·78–9·46) N m^{-2}). No significant relationship ($r^2=-0\cdot05$, $P=0\cdot36$) was shown between monthly growth rate and elasticity.

The technical success rate of echo-tracking at 85–90 per cent is high. The lack of correlation between growth rate, AAA diameter and compliance would indicate that, if compliance predicts AAA rupture, this prediction is likely to be additional to that provided by AAA diameter and growth rate.

Histological features and platelet-derived growth factor receptors in carotid atherosclerosis

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Symptoms from carotid artery atherosclerosis are dependent on the degree of stenosis and plaque composition Platelet-derived growth factor (PDGF) alters smooth muscle cell (SMC) activity. β-Receptor stimulation promotes SMC migration. α Receptors are inhibitory. Histology and PDGF receptors in symptomatic and asymptomatic plaques were studied.

Of 64 carotid artery plaques, 30 symptomatic and three asymptomatic internal carotid artery plaques removed at surgery and 31 asymptomatic post-mortem plaques were studied. The specimens were divided into three groups: symptomatic ($n=30$), asymptomatic and less than 70 per cent stenosed ($n=24$) and asymptomatic and more than 70 per cent stenosed ($n=10$). After immunochemistry, plaques were scored (0–3) for α and β receptors, PDGF protein, white blood cells, SMCs and intraplaque haemorrhage. Surface ulceration was noted.

Surface ulceration occurred in 12 symptomatic plaques and three asymptomatic plaques with more than 75 per cent stenosis ($P<0\cdot01$, Fisher's exact test). The results of PDGF receptor assessment are shown in the *Table*. The scoring reproducibility was good ($\kappa=0\cdot7$) White blood cell and intraplaque haemorrhage scores were low in the asymptomatic group with less than 70 per cent stenosis ($P<0\cdot05$, analysis of variance).

	PDGF α	PDGF β	PDGF protein
Symptomatic	1·5(0·2)*	2·2(0·2)	1·9(0·2)
Asymptomatic			
<70 per cent stenosis	2·3(0·2)	2·3(0·8)	1·4(0·2)
>70 per cent stenosis	0·9(0·3)*	1·9(0·3)	2·0(1·0)

Values are mean(s.d.). *$P<0\cdot05$ *versus* asymptomatic plaques with less than 70 per cent stenosis (analysis of variance)

Both symptomatic and asymptomatic plaques with greater than 70 per cent stenosis have low α-receptor proportions and contain high numbers of white blood cells compared with asymptomatic plaques with less than 70 per cent stenosis SMC behaviour depends on α-receptor expression, not the amount of PDGF. Ulceration was linked to symptoms, but plaque histology and expression of PDGF receptors did not indicate why stenotic plaques can produce differing symptoms

Carotid angioplasty and stenting: is it such a good idea after all?

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Initial results for carotid angioplasty have been encouraging, although randomized trials against surgery have yet to be reported The ischaemic times (balloon inflation) should be shorter than with conventional surgery, but the acute effects of angioplasty and stenting on cerebral haemodynamics are unknown. In particular, the potential for embolization during angioplasty and stenting has not been ascertained.

Thus nine patients with symptomatic internal carotid artery (ICA) stenosis greater than 80 per cent and contralateral ICA occlusion were assessed with transcutaneous Doppler ultrasonography (TCD), continuous jugular venous oximetry ($SJvO_2$) and near infrared spectroscopy (NIRS) during angioplasty and stenting Multiple emboli were detected by TCD in all patients during guidewire and stent insertion, some causing transient cerebral ischaemia (NIRS and $SJvO_2$) Furthermore, reduced middle cerebral artery velocity (MCAV) and falls in $SJvO_2$ occurred in three of the nine patients with only the guidewire *in situ*, whereas balloon inflation reduced MCAV and caused ischaemia (NIRS, $SJvO_2$) in all patients, which persisted for more than 3 min in three. Throughout angioplasty and stenting, MCAV was dependent on systemic blood pressure, reflecting poor cerebrovascular reserve in all patients.

Complications included two haematomas (retroperitoneal and groin) and two major cerebrovascular accidents (one embolic, one thrombotic occlusion of the ICA) The latter caused prolonged ischaemia (greater than 10 min), although MCAV and $SJvO_2$ recovered following thrombolysis.

These results demonstrate significant cerebral ischaemia (both haemodynamic and embolic) during angioplasty and stenting, and that the results of this technique may not be as good as at first thought. It should also be remembered that multiple embolic events may be associated with more subtle neurological complications.

Prospective randomized controlled study of ranitidine in patients with gastric cancer

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A previous study has suggested that patients with gastric cancer treated with cimetidine may have a survival advantage. This study examined the use of the more potent H_2-receptor antagonist ranitidine in patients suffering from gastric cancer Some 222 patients with gastric cancer were recruited to a multicentre prospective randomized double-blind trial comparing ranitidine 150 mg twice daily with placebo twice daily for up to 5 years The patients underwent radical or palliative resection, or were deemed inoperable at presentation. The principal outcome measures were survival and survival excluding 30-day mortality

Median (95 per cent confidence interval) survival was 331 (232–393) days in the ranitidine group compared with 187 (143–269) days in the placebo group. The difference in survival was not statistically significant ($P = 0{\cdot}22$, log rank test). When patients who died within 30 days of operation were excluded (21 in the placebo group, 15 in the ranitidine group), the difference in survival remained insignificant. No subgroup could be identified in which patients benefited significantly from treatment, but in stage IVa median survival was 134 days with placebo *versus* 313 days with ranitidine ($P = 0{\cdot}07$)

This study does not demonstrate significant benefit from the use of ranitidine in gastric cancer, but further, larger, studies may be indicated particularly in patients with stage IV disease

In vitro cancer cell microenvironmental manipulation enhances *in vivo* tumour growth

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Carbon dioxide pneumoperitoneum in laparoscopy may acidify the microenvironment of exfoliated intraperitoneal cancer cells. Acidic culture conditions increase the invasive potential of certain cancers *in vitro*, associated with induction of gelatinase or type IV collagenase This study investigated the effect of carbon dioxide exposure on *in vivo* tumour growth.

CC531s rat colonic cancer cells suspended in buffered culture medium were exposed to either 95 per cent air/5 per cent carbon dioxide (control), 100 per cent helium, or 100 per cent carbon dioxide at 15 mmHg for 3 h at 37°C. Culture medium pH and cell viability were assessed following incubation. The cells (10^5) were then injected into the peritoneal cavity of WAG rats ($n = 30$) which had undergone midline laparotomy The rats were killed at 21 days and autopsy was performed.

	Control	100 per cent helium	100 per cent carbon dioxide
Culture medium pH	7·35*	8·05	6·67
Viability (%)	>95	>95	>95
Mean(s.d.) total tumour mass (mg)	200(247)	124(116)	372(287)†

*$P < 0{\cdot}05$ *versus* 100 per cent helium and 100 per cent carbon dioxide (Student–Newman–Keuls test); †$P = 0{\cdot}01$ *versus* control and 100 per cent helium (Kruskal–Wallis analysis of variance)

Exposure to carbon dioxide pneumoperitoneum *in vitro* resulted in significant acidification of the cancer cell microenvironment without affecting cell viability. This phenomenon was associated with enhanced tumour growth after operation and may have implications for laparoscopic cancer surgery.

Circulating colorectal carcinoma cells are not invariably associated with metastasis

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The authors have previously demonstrated that tumour cells containing complementary DNA (cDNA) coding for carcinoembryonic antigen (CEA) can be identified in the circulation of patients with colorectal cancer. In this study a comparison was made of the prevalence of these cells in the circulation of patients with primary colorectal cancer with and without evidence of metastasis.

Some 14 ml of peripheral blood was sampled from patients with colorectal cancer and from 'no cancer' controls. The RNA was extracted from fractionated blood and reverse transcriptase–polymerase chain reaction performed using specific CEA primers. The 641 base pair fragment was confirmed by Southern blotting using a specific cDNA oligoprobe for CEA which lies between the two primers used.

	No. of patients	cDNA CEA positive
Control	23	0
Primary colonic cancer		
No metastases	11	7*
Metastases	17	12*

*$P < 0{\cdot}01$ *versus* control (χ^2 test)

Circulating cells expressing CEA cDNA were identified only in patients with colorectal cancer The prevalence was similar whether metastases were present or not. This suggests that circulating tumour cells may not invariably result in metastasis.

Laparotomy and laparoscopy differentially affect the development of tumour metastases

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Tumour cells are inevitably released into the systemic circulation during surgical extirpation However, not all these cells become established as metastases and the reasons for this are not fully understood. The authors have recently shown that laparoscopy and laparotomy variably suppress natural killer and lymphokine-activated killer cell function after operation and result in the differential acceleration of flank tumour growth. The aim of this study was to determine the effect of these two forms of surgical trauma on the establishment of hepatic and lung metastases in C57/BL6 female mice.

In model 1, mice ($n = 45$) each received a single cell suspension of 3×10^5 B16 melanoma cells via tail vein injection. In model 2, mice ($n = 45$) each received an intrasplenic single cell suspension injection of 1×10^6 B16 melanoma cells and their spleens were excised after allowing the cells to embolize to the liver through the portal circulation for 5 min. In each model the animals were randomized into control (anaesthetic only), laparotomy and laparoscopy groups, and these procedures were performed immediately after injection. The mice were killed 8 days later and their lungs or livers harvested to determine established pulmonary or hepatic metastases. All data are expressed as mean(s.e.m.) and analysis was with analysis of variance with least squares difference *post hoc* correction.

Model 1: Laparotomy and laparoscopy significantly enhanced the formation of pulmonary metastases (214·8(7·42) and (189·6(6·51) respectively) compared with controls (169·1(7·35)) ($P = 0·00$ and $P = 0·01$ respectively). There was also a significant difference between the laparotomy and laparoscopy groups ($P = 0·00$).

Model 2: A similar pattern was observed with a significant number of metastases established in the laparotomy (229·5(5·83)) and laparoscopy (193·9(8·11)) groups compared with controls (178·4(6·42)) ($P = 0·00$ and $P = 0·007$ respectively). There was also a significant difference between the laparotomy and laparoscopy groups ($P = 0·001$).

It appears that changes occurring after the trauma of laparotomy and, to a lesser extent, after laparoscopy significantly enhance the development of metastases from circulating tumour cells. These are due, among other factors, to the suppression of host antitumour surveillance mechanisms, which have been shown to be variably affected by these two forms of surgery.

Recruitment of non-classical lymphocytes following bacillus Calmette–Guérin immunotherapy of bladder cancer

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The aim of the study was to investigate whether $\gamma\delta$ T lymphocytes, which are known to play an important role in immunosurveillance, are involved in the successful clinical response observed following bacillus Calmette–Guérin (BCG) immunotherapy of bladder cancer.

Some 16 patients with transitional cell carcinoma (carcinoma *in situ*, pT_a–pT_2) underwent standard intravesical BCG therapy for 6 weeks. Leucocytes were isolated from patients' urine collected 12 h after the third to sixth BCG instillations, stained using pan anti-$\alpha\beta$ or anti-$\gamma\delta$ monoclonal antibodies and examined by two-colour flow cytometry. Lymphocytes in selected urinary samples were enriched by means of a magnetic separation system (Myltenyi) before phenotyping; patients' blood was examined in parallel.

For *in vitro* expansion, blood from eight healthy donors was incubated with live solubilized BCG and isopentenyl pyrophosphate (IPP; sugar derived from BCG).

All patients produced $\gamma\delta$ T cells in the urine following instillations of BCG. They could be divided into high and low producers (less than 5 per cent and 5–20 per cent of all urinary T cells respectively, $P < 0·0001$). The proportion of $\gamma\delta$ T cells increased throughout therapy ($P < 0·04$). This increase in $\gamma\delta$ T cells was local and restricted to the $V\delta2\gamma9$ subset. The *in vitro* data show that a similar expansion of $\gamma\delta$ T cells could be achieved following treatment with live or solubilized BCG or IPP, implying that IPP may serve to expand $\gamma\delta$ T cells in patients. Preliminary data suggest a trend between a high local production of $\gamma\delta$ T cells and a favourable clinical response.

In conclusion, $\gamma\delta$ T cells may play an important role in successful BCG immunotherapy of bladder cancer.

Anti-idiotypic monoclonal antibody 105AD7 increases expression of the interleukin 2 receptor by lymphocytes within colorectal cancer

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The anti-idiotypic monoclonal antibody 105AD7 has been shown to induce helper T-cell responses associated with a survival advantage in patients with advanced colorectal cancer. Interleukin (IL) 2 is an *in vivo* marker of T-cell activation and increased levels were seen in six of the original 13 patients immunized with 105AD7.

To assess whether similar immune responses could be seen at the tumour site, 12 patients with primary colorectal cancer received 105AD7 before operation. Postresection specimens were taken from normal bowel, two distinct tumour edges and the tumour centre. Immunohistochemical analysis was performed using a monoclonal antibody against the α subunit of the IL-2 receptor.

Expression was higher in immunized patients compared with that in an age- and sex-matched group with identical tumour site, stage and differentiation (median 0·77 *versus* 0·64, P not significant). A significant difference existed between the two groups in the ratio of tumour to normal bowel expression of the receptor (median 1·07 *versus* 0·42, $P < 0·02$).

These results show increased expression of the IL-2 receptor in patients receiving 105AD7, implying that 105AD7 activates T cells at the tumour site.

Production of interleukin 5 following bacillus Calmette–Guérin immunotherapy of bladder cancer

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The aim of the study was to establish whether the success of intravesical bacillus Calmette–Guérin (BCG) immunotherapy of transitional cell carcinoma of bladder is due to the preferential induction of a 'classical' local T helper 1 (T_H1) cytokine response.

Some seven patients with carcinoma *in situ* received standard intravesical BCG therapy (six consecutive weekly instillations of Evans strain of BCG). Urine voided during the 12 h after instillation was centrifuged, dialysed overnight and assayed for interleukin (IL) 5, as well as for IL-2, IL-8, IL-10, tumour necrosis factor (TNF) α, interferon (IFN) γ and soluble intercellular adhesion molecule (sICAM) 1 using commercial enzyme-linked immunosorbent assays.

Following therapy, local production of IL-5 by all patients was observed. Although the onset and degree of IL-5 production varied among patients, in general both the concentration and total amount increased throughout therapy ($P < 0·05$). Furthermore, a strong correlation was observed between the production of IL-5 and IL-10 ($P < 0·001$) or sICAM-1 ($P < 0·01$), but not with IL-2, IL-8, TNF-α or IFN-γ. In contrast, IL-10 production significantly correlated with the production of all cytokines ($P < 0·05$ and $P < 0·01$ respectively for IL-8 and all other cytokines).

In conclusion, the detection of a classical T_H2 cytokine, IL-5, in the urine of all patients examined indicates that BCG cancer immunotherapy does not induce solely a T_H1 response but rather a T_H1–T_H2 or T_H0 response. The correlation between IL-5, sICAM-1 or IL-10 secretion implies a connection in their production.

Jass score, immune suppression and interleukin 12 production: a functional link

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Interleukin (IL) 12 is a heterodimeric cytokine produced principally by cells of monocyte–macrophage lineage. Its main mode of action is thought to be by upregulation of interferon γ. IL-12 acts as a growth factor for activated natural killer (NK) and T cells, enhancing the cytotoxic activity of NK cells and favouring cytotoxic T-cell generation. Animal experiments have demonstrated the role of IL-12 in stimulating a cell-mediated antitumour response. The aim of this study was to investigate whether preoperative IL-12 levels are associated with a human antitumour immune response.

Preoperative peripheral blood mononuclear cells from patients with colorectal cancer and age-matched controls were stimulated by *Staphylococcus aureus* Cowan's strain 1 (0·0075 per cent weight per volume) *in vitro* for 24 h Expression of IL-12 was then assessed by enzyme-linked immunosorbent assay. A single pathologist assessed the tumour for stage according to the Jass, tumour node metastasis and Dukes classification.

Twenty-eight patients with colorectal cancer and six controls were recruited. Lymph node-negative tumours ($n = 19$) were significantly associated with the presence of detectable IL-12 ($P = 0\cdot04$). In addition, significantly higher levels of IL-12 were detected in patients whose tumours manifested a lymphocytic infiltrate ($n = 18$) on histological examination ($P = 0\cdot05$).

This study represents the first demonstration of a relationship between Jass score and functional measurements of immune suppression. The impaired production of IL-12 in patients without a lymphocytic response may allow selection of patients for treatment with exogenous IL-12.

Familial desmoid disease due to a 3′ truncating mutation of the familial adenomatous polyposis gene

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Chain-terminating mutations at the familial adenomatous polyposis (FAP) gene are responsible for FAP, most mutations being in the 5′ half of the gene. This leads to truncation of the normal 312-kDa protein into shorter polypeptides. The authors describe a large kindred over three generations with dominantly inherited familial desmoid disease.

The index case, who had extensive paraspinal desmoids, presented with a mesenteric desmoid necessitating removal of 90 per cent of the small bowel. Chromosomal analysis of this tumour revealed a 5q deletion in the region of the FAP gene.

Linkage analysis was then carried out in the entire kindred using microsatellite markers. This showed that the completely penetrant desmoid phenotype was linked to the FAP gene. None of the kindred had polyposis but one had died from periampullary cancer. The affected copy of the FAP gene was then cloned. A protein truncation assay was then performed, which revealed that the cloned gene transcribed a truncated protein product. The 3′ end of the gene was directly sequenced and this showed a frameshift mutation in codon 1924, resulting in a premature stop codon.

Thus, familial desmoid disease may be due to a 3′ mutation in the FAP gene and these patients need not have the polyposis phenotype.

Colonic cell apoptosis is independent of MSH2 status following DNA damage by methylnitronitrosoguanidine

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Hereditary non-polyposis colorectal cancer (HNPCC) is a familial cancer syndrome accounting for 5–10 per cent of all colorectal cancers. Affected patients carry germline mutations in one of the DNA mismatch repair enzymes, and develop early-onset right-sided colorectal cancers. Inactivating mutations in the DNA mismatch repair enzyme MSH2 (mut S homologue 2) are found in over half of all HNPCC cases. Little is known about the responsiveness of this subset of colorectal tumours to chemotherapeutic agents.

This study investigated whether the MSH2 enzyme can couple DNA damage induced by methylnitronitrosoguanidine (MNNG) to an apoptotic pathway (MNNG is a potent carcinogen known to induce nucleotide mismatches that are repaired by the MSH2 enzyme).

Transgenic mice that were wild-type, heterozygous or homozygous for a deletion in the MSH2 gene were injected intraperitoneally with various doses of MNNG. Colons were harvested and fixed 6 h following injection. The prevalence of apoptotic bodies in 50 colonic crypts was scored by microscopy.

	Prevalence of apoptosis in colonic crypts			
	Dose of MNNG (mg kg^{-1})			
MSH2 genotype	0	25	50	100
Wild-type ($n = 4$)	0·5(0·5)	2·75(0·85)	3·75(1·03)	10·25(2·78)
Heterozygotes ($n = 4$)	0(0)	2·5(0·87)	3·4(1 29)	7·0(2·38)
Homozygotes ($n = 4$)	0·25(0·25)	3·75(2·14)	4·3(2·40)	9·5(2·60)

Values are mean(s.e.m.). $P = 0\cdot68$ between genotypes (analysis of variance)

The prevalence of colonic cell apoptosis is independent of MSH2 genotype following DNA damage by MNNG. Therefore, the DNA mismatch repair enzyme MSH2 is not required for the induction of apoptosis in the colon following MNNG administration. Thus tumours from individuals with HNPCC are likely to be responsive to chemotherapeutic compounds that induce DNA mismatches as their primary mode of action.

Expression of *reg* in early-stage colorectal cancer predicts death

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Human *reg* gene transcripts have been identified in a majority of colorectal adenocarcinomas *reg* expression in colonic and rectal tumours is compared and the influence of expression status on cancer-specific death in N_0 and N_1 disease determined.

RNA was extracted from 143 frozen specimens of colonic and rectal adenocarcinoma using the cationic surfactant method. Reverse transcriptase–polymerase chain reaction was carried out using primers to identify *reg* gene transcripts. The colonic cancer cell line SW948 was used as a positive control for expression. Full clinical follow-up data for a minimum of 1 year (range 12–72 months, mean 45·3 months) were available for 69 of the patients who had undergone potentially curative surgery (M_0). Patients dying from non-cancer-related causes were excluded from the study. The results are shown in the *Tables*.

Carcinoma	*reg*-positive carcinoma	*reg*-negative carcinoma
Colon	40 (45)	44 (55)
Rectum	39 (66)	20 (34)*

Values in parentheses are percentages. *$P < 0\cdot05$ *versus reg*-positive rectal carcinoma (χ^2 test with Yates' correction) *reg* is expressed more commonly in rectal than in colonic cancer

Stage	*reg*-positive carcinoma death	*reg*-negative carcinoma death
T_{1-3}, N_1, M_0	11 of 20 (55)	7 of 14 (50)
T_{1-3}, N_0, M_0	6 of 15 (40)	2 of 21 (10)

Values in parentheses are percentages. $^*P < 0{\cdot}05$ *versus reg*-positive death in N_0 disease (logistic regression)

reg expression was found not to predict outcome in N_1 tumours, but did predict recurrence and cancer-specific death in N_0 disease. These results confirm the ectopic expression of *reg* in the majority of a large series of tumours and demonstrate a difference between colonic and rectal tumours at a cellular level. In addition, *reg* status significantly predicts disease-specific death in localized colorectal cancer.

Cytokine interactions in ulcerative colitis and in a human colonic cell line HT-29

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Cytokines are key mediators of the inflammatory response in ulcerative colitis (UC) but interactions between cytokines are poorly understood. A study was therefore made of interleukin (IL) 1β, IL-8, IL-15 and interferon (IFN) γ in patients with UC and in HT-29 colonic cell lines.

Using reverse transcriptase–polymerase chain reaction an analysis was carried out of IL-1β, IL-8, IL-15 and IFN-γ messenger RNA (mRNA) expression in rectal biopsies ($n = 25$) taken sequentially from ten patients with UC in relapse and remission. In addition, cytokine expression was investigated in HT-29 cells under basal conditions and following stimulation with IL-1 or IFN-γ for 1, 6 and 24 h.

Of the 25 rectal biopsies studied, IL-β was expressed in 20, IL-8 in 18, IL-15 in ten and IFN-γ in nine. A correlation was apparent between IL-1β and IL-8 gene expression ($\chi^2 = 7{\cdot}88$, $P < 0{\cdot}005$) and between IL-15 and IFN-γ gene expression ($\chi^2 = 8{\cdot}36$, $P < 0{\cdot}005$). In HT-29 cells, IL-1 induced IL-8 expression at all time points studied, whereas IFN-γ stimulated IL-8 expression at 6 h only. IFN-γ induced IL-15 expression at all time points, whereas IL-1 stimulated IL-15 expression at 6 h only.

In rectal biopsy samples from patients with UC an association was found between IL-1β and IL-8 mRNA expression, and similarly between IL-15 and IFN-γ mRNA expression. *In vitro* data suggest the mechanism may be the induction of IL-8 by IL-1 and of IL-15 by IFN-γ.

Role of nitric oxide in non-adrenergic non-cholinergic relaxation of human colon and stomach circular muscle

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Variations in nitric oxide (NO) production or NO synthase activity have been reported in certain diseases (e.g. Hirschsprung's disease and pyloric stenosis). However, the exact nature of the inhibitory non-adrenergic non-cholinergic (NANC) neurotransmitter(s) in the normal tissue has not been fully characterized. This study investigated the contribution of NO to NANC relaxation in macroscopically normal specimens of human colonic and gastric circular muscle, using the NO synthase inhibitors N^G-nitro-L-arginine (L-NOARG) and N^G-nitro-L-arginine methyl ester (L-NAME). Ascending and sigmoid colon were examined separately to explore regional variations within the colon.

NANC relaxation in response to electrical field stimulation was markedly inhibited by L-NAME and L-NOARG in ascending and sigmoid colon (greater than 80 per cent) and in gastric antrum and body (100 per cent) Mean(s.d.) L-NAME and L-NOARG IC$_{50}$ values in ascending colon were respectively 9·6(2·1) μmol l^{-1} ($n = 5$) and 2·8(0·9) μmol l^{-1} ($n = 5$), and in sigmoid colon 23(8) μmol l^{-1} ($n = 5$) and 3·7(0·7) μmol l^{-1} ($n = 4$). In stomach mean(s.d.) IC$_{50}$ values for L-NAME and L-NOARG were 4·3(2·1) μmol l^{-1} ($n = 3$) and 0·4(0·2) μmol l^{-1} ($n = 4$) respectively. No significant difference in IC$_{50}$ values of the inhibitors was found between colonic regions. However, values for L-NOARG were significantly different in colon and stomach ($P = 0{\cdot}05$ and $P = 0{\cdot}005$ for ascending and sigmoid colon respectively) A rise in colonic muscle tone in the presence of L-NAME and L-NOARG may indicate a tonic production of NO.

It is suggested that NO may be a principal mediator of NANC relaxation in the circular muscle of human colon and stomach.

Absent pacemaker cells in children with anorectal anomalies: the cause of their constipation?

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Constipation is a frequent functional problem in children following correction of congenital anorectal malformations. This has been assumed to be due to hypomotility of the rectosigmoid colon; however, segmental colonic motility studies have demonstrated generalized colonic hypomotility in children with a high anorectal anomaly The cause of this disorder is unknown.

The aim of this study was to determine whether the observed colonic hypomotility seen in patients with anorectal malformations is due to defects in distribution or density of interstitial cells of Cajal (ICCs), recently identified as 'intestinal pacemaker cells'.

Colostomy specimens from eight patients with high anorectal anomalies (aged 2–14 months) and from four control patients with non-motility-related gastrointestinal pathology (aged 1–4 months) were studied. Specimens were labelled immunohistochemically by means of dual fluorescence with antibodies to PGP 9.5, a marker for neural tissue, and to c-*kit*, a recently characterized marker for ICCs.

Ganglion cell disorders were excluded in all patients. In four of eight patients with anorectal malformation, ICCs were completely absent. Only two patients with anomalies and all controls had a normal distribution of ICCs.

These preliminary findings suggest that defects in the population of intestinal pacemaker cells may underlie the colonic hypomotility seen with high anorectal malformations and may be the source of refractive constipation.

Development of a genetic detection assay for colorectal cancer micrometastases

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An accurate predictor of outcome for colorectal cancer remains elusive. It was decided to develop a sensitive polymerase chain reaction (PCR)-based assay to detect minimal residual disease which exploits cancer-specific gene mutations. With ethical approval and informed patient consent, bone marrow aspirates, peripheral blood, portal blood and tumour tissue were collected from 51 patients (40 with primary colorectal tumours, five who had resection of colorectal liver metastases, and six benign cases as controls).

For comparison with immunocytochemical strategies reported previously, bone marrow cytospins were stained for cytokeratin (CK) 18. Preliminary results showed a high CK-18 rate of positivity (12 of 19 cases) with substantial observer dependence. None of the control cases examined was positive. There was no association between CK-positive staining and Dukes stage, nor with disease-free survival.

For the genetic assay, tumour-specific mutations were first identified by molecular analysis. Some 38 tumours had mutations, with eight at K-*ras* codons 12 and 38 in the adenomatous polyposis coli gene Results of molecular analysis for each tumour were used to devise techniques for low-level mutation detection in blood and bone marrow. PCR-generated restriction enzyme sites specific to particular mutations were created. This allows sequential amplification of mutant sequences and automated DNA analysis. In initial dilution experiments one mutant cell in 10^4 normal cells was detected with non-radioactive techniques.

These results indicate that genetic-based assays are tumour specific, allow automation and avoid operator dependence.

Effect of butyrate on the growth of colonic carcinoma cells

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Short-chain fatty acids, particularly butyrate, have received much attention recently as dietary components that are potential regulators of differentiation and proliferation in the large bowel. In this study the effects of butyrate on two colonic carcinoma cell lines, HT29 and CaCo2, were evaluated.

Initial findings suggested that, at concentrations greater than $1\ \mathrm{mmol\ l^{-1}}$, butyrate significantly suppressed the size of cell populations adherent to culture dishes. With $5\ \mathrm{mmol\ l^{-1}}$ butyrate, this effect was observed from day 1 following butyrate challenge, and by day 7 the adherent cell population in butyrate-treated cultures was less than 10 per cent that of the controls. Further examination of the effects of butyrate, on both adherent and non-adherent populations, suggested that butyrate treatment induced cellular detachment from adherent populations as well as growth suppression.

To define the processes underlying these observations, an evaluation was made of the effects of butyrate on the expression of genes involved in apoptosis (transforming growth factor (TGF) β_1, β_2 and β_3) and cell cycle control (*Waf1/Cip1*). Using Northern blot analysis, the expression of these genes was examined across time courses following butyrate treatment in both cell lines.

The study demonstrated that expression of the TGFs was unaffected by butyrate challenge during the first 24 h following treatment, suggesting that induction of this growth factor family was not required in response to butyrate in these cell lines Waf1 was very significantly induced by butyrate challenge in both cell lines at the 3-, 6- and 24-h time points following treatment. This observation links the growth suppression observed in response to butyrate with a known mechanism for interruption of the cell cycle

Effect of the surgeon's specialty interest on outcome after curative colorectal cancer surgery

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The authors have shown previously that surgeons of different specialty interests perform different types of resection, varying from segmental to radical resection, for colorectal cancer. The aim of this study was to assess whether the surgeon's specialty interest had any effect on outcome following curative colorectal cancer surgery.

Between 1990 and 1993, 254 patients underwent curative colorectal cancer surgery, of which 123 operations were performed by surgeons with a colorectal cancer interest, 73 by general surgeons and 58 by surgeons with a vascular or transplant interest. Patient outcome with a minimum follow-up of 3 years is shown in the *Table*.

	Recurrence rate (%)	
Surgeon group	Local	Overall
Colorectal cancer interest	11	24
General surgeon	30*	48†
Vascular or transplant interest	12	25

$^*P = 0{\cdot}001$, $^†P = 0{\cdot}003$ *versus* other surgeon groups

There were no differences in Dukes stage, emergency *versus* elective surgery or postoperative mortality rates between groups. These findings demonstrate that surgeons without a declared specialty interest perform significantly poorer when managing patients with colorectal cancer.

Pathways in the evolution of early colorectal carcinoma: histological and genetic analysis

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It has been reported that there are two major pathways in the evolution of colorectal carcinoma: via polypoid-type early cancer (PTEC) and via superficial-type (flat type) early cancer (STEC). Among 1635 neoplastic lesions removed in a recent colonoscopic series, 77 carcinomas were limited to the mucosa and 30 showed submucosal invasion. Of these 107 carcinomas, the proportion of STEC was 18 per cent, much lower than that of 72 per cent for PTEC.

In an analysis of 95 carcinomas with submucosal invasion, including surgical specimens, 19 per cent were considered to be of superficial type in origin and 81 per cent to be of polypoid type. These data indicate the predominance of PTEC in early colorectal carcinomas

In an analysis of Ki-*ras* point mutations, the frequency of mutation in STEC was significantly lower than that in PTEC (three of 21 *versus* 17 of 34) An analysis of replication error (RER) using microsatellite markers was carried out in 45 sporadic colorectal carcinomas in early stages. RER tended to be more frequent in STEC than in PTEC, and in lesions of the right colon RER was significantly more common in STEC than in PTEC (four of nine *versus* none of ten, $P < 0{\cdot}05$).

These results suggest differences in genetic alterations between polypoid-type and superficial-type colorectal carcinomas in early stages, supporting the existence of different pathways in the evolution of colorectal carcinoma.

Taurine attenuates interleukin 2-induced vascular injury through a calcium-dependent effect on interleukin 2-activated lymphocytes

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Recombinant interleukin (rIL) 2 immunotherapy is limited by microvascular endothelial cell (EC)-targeted injury. The interaction between rIL-2-activated lymphoid cells and ECs is a possible mechanism of this systemic toxicity. The authors have previously demonstrated that the amino acid taurine, a known modulator of Ca^{2+} channel permeability, can significantly attenuate rIL-2-induced EC injury without compromising its tumoricidal ability. Having established that this observed effect of taurine on lymphocyte-mediated EC cytotoxicity was Ca^{2+} dependent, a series of experiments was carried out to examine directly the effects of taurine on intracellular Ca^{2+} concentration $[Ca^{2+}]_i$ in lymphocytes while conjugated to ECs or tumour targets (DAUDI) using a flow cytometric assay with the calcium-sensitive dye Fluo-3. The effect of taurine on Ca^{2+}-dependent granule exocytosis induced by phorbol myristate acetate (PMA)/A23187 was also examined by measuring cytotoxic granule protein (BLT esterase) activity.

Results indicated that $[Ca^{2+}]_i$ in lymphokine-activated killer (LAK) cells cultured in taurine rose more rapidly following conjugation to ECs and remained at a higher level throughout the study period than that in a control group. By contrast, $[Ca^{2+}]_i$ in LAK cells cultured with taurine and subsequently conjugated with a tumour target (DAUDI) was not significantly different from control levels. These findings may explain the ability of the same effector cell to mediate enhanced lysis of one target cell (tumour) yet attenuate lysis of another (EC). BLT esterase production from LAK cells following stimulation with PMA/A23187 was raised following incubation with taurine, indicating that these cells may have greater cytotoxic capacity. Intracellular calcium antagonists TMB-8 and EGTA inhibited BLT esterase production in a concentration-dependent manner, indicating that these cells retained their capacity for calcium-dependent granule exocytosis.

Thus, taurine behaves as an attenuator of rIL-2-induced vascular injury through a Ca^{2+}-dependent mechanism involving enhanced $[Ca^{2+}]_i$, and also has the capacity to increase cytotoxic granule levels in stimulated LAK cells.

Patients with severe acute pancreatitis and sepsis have increased priming of peripheral blood neutrophils

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Cytokine-driven neutrophil activation has been implicated in the pathophysiology of early organ failure in severe acute pancreatitis and sepsis. Little is known, however, of the functional status of neutrophils, and no study has directly compared neutrophil function in these conditions.

Neutrophil function was studied in ten patients with severe sepsis (median Acute Physiology And Chronic Health Evaluation (APACHE) II score 12 (interquartile range (i.q.r.) 10–16)) and in 23 with severe acute pancreatitis (median APACHE II score 10 (i.q.r. 9–12)), and values were compared with those in healthy controls. On day 1 of illness, quantitative measurement of oxidative burst in peripheral blood neutrophils was determined by flow cytometric analysis of intracellular cleavage of non-fluorescent 2′7′-dichlorofluorescein to highly fluorescent 2′7′-dichlorofluorescein following the addition of phorbol myristate acetate. Using this method, the proportion of primed neutrophils in the peripheral circulation was also determined.

	Total fluorescence (%)	Primed neutrophils (%)
Controls	173 (128–226)	11·7 (6·3–19·7)
Pancreatitis	262 (200–330)	24·2 (19·3–29·5)
Sepsis	336 (220–1001)	29·1 (18·2–37·2)

Values are median (i.q.r.)

A greater neutrophil oxidative burst was observed in patients with sepsis ($P = 0·02$) and severe pancreatitis ($P = 0·05$) than in healthy controls (Mann–Whitney U test). The percentage of primed peripheral blood neutrophils was also higher in both patient groups (pancreatitis $P = 0·007$, sepsis $P = 0·009$) than in controls.

These results support the hypothesis that neutrophils are involved in the development of systemic complications in these conditions

Vascular adhesion protein 1 and intercellular adhesion molecule 1 mediate T-cell binding to human hepatocellular carcinoma

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Human hepatocellular carcinomas (HCCs) are heavily infiltrated by T cells, which enter tumour tissue after recognizing and binding to tumour endothelium. A greater understanding of the molecules that regulate this process will shed light on the pathogenesis of the antitumour immune response and will have important implications for the development of adoptive immunotherapy. The aim of this study was to determine the molecular mechanisms of T-cell adhesion to endothelium in human HCC

Tumour tissue was obtained at hepatic resection from ten patients with HCC and from ten with colorectal hepatic metastasis (CHM). Tumour-infiltrating lymphocytes (TILs) were isolated and expanded in recombinant interleukin 2. *In situ* proliferation of TILs was determined by double staining for the nuclear proliferation antigen Ki-67 and anti-CD3. Immunohistochemistry and two-colour flow cytometry were used to study adhesion molecule expression on TILs and tumour endothelium, and a tissue-binding assay was used to determine the functional pathways of TIL adhesion to endothelium on vessels in tissue sections from HCC and adjacent non-involved liver tissue

In both tumours less than 5 per cent of CD3-positive T cells were also positive for Ki-67, suggesting that ongoing recruitment rather than local proliferation is responsible for the infiltrate. CD3-positive TILs had high values for leucocyte functional antigen 1 and very late activation antigen 4 but low values for CD62L, $\alpha 4\beta 7$ and αIEL$\beta 7$. The endothelium in HCC vessels was strongly positive for intercellular adhesion molecule (ICAM) 1 and vascular adhesion protein (VAP) 1, whereas CHM vessels were weakly positive for ICAM-1 and were VAP-1 negative. Vessels in both tumours expressed low levels of vascular cell adhesion molecule 1 but were negative for CD62E. To determine whether endothelial ICAM-1 and VAP-1 have a functional role in TIL binding to HCC vessels, binding of TILs to tumour endothelium was assessed in tissue sections from four patients with HCC. TIL binding to tumour vessels was inhibited by monoclonal antibodies against either VAP-1 or ICAM-1. Mean(s.d.) TIL binding to HCC (as a percentage of maximum binding) was· control monoclonal antibodies 100 per cent; anti-VAP-1 62(27) per cent; anti-ICAM-1 51(11) per cent; anti-VAP-1 and ICAM-1 48(7) per cent

In conclusion, TILs are actively recruited to liver tumours and the high expression of ICAM-1 and VAP-1 on vessels in HCC is associated with functional binding of TILs to both of these molecules on tumour endothelium VAP-1 is expressed selectively on endothelium in HCC, suggesting that tissue-specific pathways might mediate TIL recruitment. In addition, the fact that HCC and CHM differ in their expression of endothelial adhesion molecules suggests that local tumour factors, rather than the anatomical site of the tumour, determine the phenotype of tumour endothelium.

Free radical production by peripheral blood mononuclear cells is increased in severe acute pancreatitis but not in sepsis

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Increased production of proinflammatory cytokines by peripheral blood mononuclear cells has been demonstrated in patients with severe acute pancreatitis. The cascade of events resulting from cytokine release has been implicated in the development of early organ failure. The direct effects of circulating monocytes in terms of oxidative burst and free radical production have not been studied previously.

Monocyte function was compared in ten patients with severe sepsis (median Acute Physiology And Chronic Health Evaluation (APACHE) II score 12 (interquartile range (i.q.r.) 10–16)) and in 23 with severe acute pancreatitis (median APACHE II score 10 (i.q.r. 9–12)), and with values in healthy controls. On day 1 of illness, quantitative measurement of oxidative burst in peripheral blood monocytes was determined by flow cytometric analysis of intracellular cleavage of non-fluorescent 2′7′-dichlorofluorescein to highly fluorescent 2′7′-dichlorofluorescein following the addition of phorbol myristate acetate.

	Total fluorescence
Controls	77 (51–216)
Acute pancreatitis	258 (107–296)
Sepsis	61 (38–251)

Values are median (95 per cent confidence interval)

A significantly greater monocyte oxidative burst was observed in patients with severe acute pancreatitis but not in those with sepsis, compared with healthy controls ($P = 0{\cdot}011$, Mann–Whitney *U* test). This suggests that these cells may have an important role to play in both cytokine production and in the direct cellular damage that occurs as part of an excessive systemic inflammatory response.

Early changes in intestinal permeability seen in patients with severe acute pancreatitis

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The role of the gut in the pathogenesis of sepsis in acute pancreatitis remains controversial. Mucosal damage occurring during the acute episode may alter the integrity of the gut mucosal barrier, resulting in endotoxaemia and bacterial translocation. An increase in permeability to macromolecules may contribute to multiple organ system failure and later septic complications

To test this hypothesis, a prospective study of consecutive patients admitted with acute pancreatitis was carried out. Once a diagnosis had been made, patients were divided into mild and severe groups on the basis of pancreatic computed tomography assessment. Intestinal permeability was determined within 48 h of admission, using a differential polyethylene glycol (PEG) absorption technique. PEG 3350 and PEG 400 were given as orally administered probes.

All patients were also compared with a healthy control population. Results of PEG retrieval are expressed as median (interquartile range) and analysed with the Mann–Whitney *U* test.

	No. of patients	PEG 400 (%)	PEG 3350 (%)
Mild pancreatitis	13	14·7 (10·7–18·9)	0·07 (0·06–0·14)
Severe pancreatitis	12	21·4 (10·5–38·3)	0·56 (0·27–1·52)*
Controls	12	18·0 (15·8–21·8)	0·11 (0·08–0·15)

$^*P < 0{\cdot}01$ *versus* mild pancreatitis and controls

Intestinal permeability to PEG 3350 was significantly increased in patients with severe acute pancreatitis when compared with both patients with mild disease and controls. The four patients who died from the disease exhibited higher permeability than the rest of those with severe pancreatitis, although this was not statistically significant.

Using this novel method, patients with severe acute pancreatitis have been shown to have increased intestinal permeability to macromolecules. This study strongly supports earlier animal work implicating increased gastrointestinal permeability in the aetiology of pancreatic sepsis.

Phenotypic and functional analysis of fresh and recombinant interleukin 2-cultured tumour-infiltrating lymphocytes from human malignant liver tumours

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T cells mediate specific antitumour responses to several solid tumours, but little is known about the functional characteristics of tumour-infiltrating lymphocytes (TILs) derived from human liver tumours. Although hepatocellular carcinomas (HCCs) are invariably infiltrated by T cells, the tumour has a poor prognosis suggesting that T cells infiltrating HCC are functionally suppressed. To address this hypothesis, the phenotypic and functional characteristics of TILs derived from primary HCC and colorectal hepatic metastasis (CHM) were investigated

TILs were isolated from resected tumours and studied either fresh or after *in vitro* expansion by co-culturing with autologous tumour cells in 1000 units ml^{-1} recombinant interleukin (rIL) 2. Two-colour flow cytometry was used to determine expression of the lineage markers CD3, CD4, CD8, CD14 and CD57, and of the activation antigens CD25, CD71, CD69 and human leucocyte antigen (HLA)-DR. Cytotoxicity against autologous, allogeneic, K562 and Daudi tumour targets was assessed by 4-h chromium release assays.

Fresh TILs comprised CD3$^+$ (mean(s.d.) 66(6) per cent), CD4$^+$ (57(8) per cent), CD8$^+$ (22(5) per cent), CD14$^+$ (18(6) per cent) and CD57$^+$ (20(5) per cent) cells in HCC, and CD3$^+$ (72(11) per cent), CD4$^+$ (50(13) per cent), CD8$^+$ (21(2) per cent), CD14$^+$ (37(9) per cent) and CD57$^+$ (23(6) per cent) in CHM In both tumours, fresh TILs were high in HLA-DR (71(9) per cent) and CD69 (64(9) per cent) but low in L-selectin (4(1) per cent) compared with autologous PBLs (25(7) per cent, 5(1) per cent and 66(6) per cent respectively). TILs could be expanded more than 1000-fold in IL-2 without further restimulation with autologous tumour cells; the CD4:CD8 ratio was maintained but the proportion of CD57$^+$ cells increased to 30(11) per cent in HCC and to 41(6) per cent in CHM. Fresh TILs displayed no cytotoxicity against tumour targets. Cultured HCC TILs and CHM TILs differed in the target cells they could lyse. Results of antitumour cytotoxicity at an effector:target ratio of 40:1 expressed as the mean(s.d.) percentage of specific lysis:

(i) Cultured HCC TILs: autologous target 69(7); Daudi 46(21); K562 48(16)
(ii) Cultured CHM TILs: autologous target 15(5); Daudi 73(5); K562 65(5)
(iii) rIL-2 expanded HCC PBLs: autologous 45(2); Daudi 57(9); K562 54(4)

In summary, (1) fresh TILs from human liver tumours are predominantly activated T cells with a high CD4 : CD8 ratio that express HLA-DR and CD69; (2) fresh TILs do not lyse tumour targets but this functional deficiency can be reversed by culture in high-dose IL-2; (3) CHM TILs show non-specific cytotoxicity against allogeneic, Daudi and K562 tumour targets, whereas HCC TILs lyse autologous tumour cells, suggesting that a tumour-specific T-cell response exists in HCC.

In conclusion, HCC TILs are functionally suppressed, which might explain their failure to prevent tumour progression *in vivo*. The fact that this suppression is reversible suggests that cultured TILs have potential in the adoptive immunotherapy of HCC.

Wound complications following major abdominal surgery in human immunodeficiency virus-seropositive patients

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Between April 1986 and April 1996, 1060 human immunodeficiency virus (HIV)-positive patients have been referred for surgery, of which 64 have undergone laparotomy The hospital records of these 64 patients were reviewed for the incidence of wound complications and wound dehiscence, as well as for age, sex, CD4 count, preoperative haematology and biochemistry findings, and histology findings. These HIV cases were compared with matched HIV-negative controls who had undergone laparotomy in the same hospital during the same period.

There was a significantly greater number of total wound complications ($P = 0{\cdot}0004$) and wound dehiscence ($P = 0{\cdot}003$) in the HIV group compared with the control group. No correlation was demonstrated between CD4 count or albumin and wound dehiscence, but the presence of intra-abdominal malignancy found at laparotomy significantly increased the chances of wound failure.

The risk of wound complications and poor wound healing following laparotomy in HIV-seropositive patients is higher than in HIV-negative controls. The development of postoperative wound problems cannot be predicted from the preoperative assessment. However, the presence of intra-abdominal malignancy found at laparotomy in HIV-positive patients significantly increases the likelihood of wound problems and dehiscence. These results are consistent with previous reports suggesting that wound healing is interfered with in the presence of acquired immune deficiency syndrome in patients with anorectal disease.

Value of nutritional support in the perioperative period: an analysis of randomized controlled trials

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Recent studies have shown that malnutrition occurs in up to 30 per cent of patients undergoing gastrointestinal surgery These patients are at increased risk of morbidity and mortality in the postoperative period. Nutritional support has been given in the perioperative period with the aim of reducing postoperative morbidity and mortality.

The aim of the present study was to evaluate the randomized controlled trials of nutritional support (parenteral, enteral and specific nutrients) in the perioperative period.

Fifty prospective randomized controlled trials published between 1980 and 1996 were identified. Thirty trials (2673 patients) evaluated the use of parenteral nutrition, 14 studies (811 patients) examined the effects of enteral nutritional support and six (631 patients) evaluated the use of combinations of key nutrients (L-arginine, n-3 essential fatty acids and RNA) For each trial included in the study, the observed odds ratio (and 95 per cent confidence interval) of the outcome measures (infectious complications, major complications and mortality) were determined. The results of the individual studies were combined using standard statistical methodology, to produce a combined odds ratio for each of the outcome variables.

The results suggest that the use of parenteral nutrition in the perioperative period does not result in clinical benefit. However, the provision of enteral nutrition and combinations of specific nutrients, although not affecting mortality, does result in a significant reduction in the likelihood of both major complications and infectious complications

Tri-iodothyronine shows synergism with isoprenaline in septic myocardium

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Acute changes in metabolic processes diminish the availability of tri-iodothyronine (T_3) in a variety of stress states. T_3 has been reported to reduce inotrope requirements following cardiopulmonary bypass. Current interest surrounds its potential role in sepsis. Whether T_3 acts directly or by interaction with the adrenergic receptor is uncertain This study aimed to delineate the effects of T_3 administration on myocardial contraction and adrenergic response in endotoxaemia.

Atria were isolated from male Sprague Dawley rats following 24 h continuous intravenous infusion of either *Escherichia coli* endotoxin (1 mg kg^{-1}) or vehicle ($n = 6$). Force and rate of contraction were measured in an organ bath by an isometric force transducer. Measurements were made at baseline and in response to T_3 (440 nmol l^{-1}). Following re-equilibrium (return of rate to baseline) the responses to isoprenaline and to a further increment of T_3 (280 nmol l^{-1}), added during the isoprenaline response, were measured. Values are mean(s.e.m.); statistical comparison was by unpaired *t* test.

The myocardial depressant effect of endotoxin was apparent at baseline, with a force of contraction of $3{\cdot}04(0{\cdot}32) g \times 10^{-1}$ *versus* $4{\cdot}41(0{\cdot}67) g \times 10^{-1}$ in controls ($P < 0{\cdot}01$) Following T_3 administration an increase in force of contraction occurred in both groups, but the effect was less in the endotoxin-exposed atria ($1{\cdot}42(0{\cdot}14)$ *versus* $2{\cdot}14(0{\cdot}67) g \times 10^{-1}$, $P < 0{\cdot}05$). The inotropic response to isoprenaline was increased in endotoxic atria compared with controls ($4{\cdot}26(0{\cdot}15)$ *versus* $3{\cdot}54(0{\cdot}12)$, $P < 0{\cdot}01$). T_3 with isoprenaline had an additional inotropic effect, comparable in endotoxic atria and controls ($1{\cdot}00(0{\cdot}07)$ *versus* $0{\cdot}93(0{\cdot}12)$, *P* not significant)

In endotoxic atria the direct inotropic effect of T_3 is diminished; however, following T_3 exposure the response of endotoxic atria to adrenergic agonist is increased in comparison with controls. In addition, when combined with isoprenaline the T_3 response in endotoxic atria is restored. It is concluded that T_3 displays synergism with β-adrenergic agonist in endotoxin-exposed myocardium This effect may merit further study as a means of supporting the failing adrenergic response in sepsis.

Cytotoxicity of electrosurgical smoke in minimal access surgery

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Exfoliated cancer cells from the primary tumour have been implicated in port-site recurrence after ablative procedures for cancer using minimal access surgery. During these procedures the intraperitoneal environment is exposed to the insufflating gas and smoke produced by pyrolysis of fat and protein as a result of the interaction of high-frequency electrosurgery with tissue.

The aim of the study was to investigate the survival of cancer cells exposed to an inert gas with or without smoke produced by pyrolysis.

In vitro culture medium (Dulbecco's modified Eagle's medium (DMEM)-S12) was exposed to a helium atmosphere with or without smoke produced by pyrolysis for 30 min. Smoke was produced by a standardized application of high-frequency electrosurgery on fresh porcine liver and layered on to the culture medium with a Buchi evaporator. MCF7 breast cancer cells were incubated in serial dilutions of the 'smoked' culture medium for 15 min, after which they were transferred to fresh culture medium. A clonogenic assay was then performed.

The 'smoked' culture medium reduced the clonogenicity of the MCF7 cancer cells by 70 per cent in a concentration-dependent manner in comparison to controls.

In conclusion, high concentrations of smoke produced by high-frequency electrosurgery applied during minimal access surgery is cytotoxic to cancer cells

Viability of airborne cancer cells released by ultrasonic cavitation and electrosurgery

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The implantation of viable cancer cells exfoliated during tumour resection substantially reduces the likelihood of cure. The ultrasonically activated scalpel utilizes mechanical energy to disrupt tissues by cavitation and is increasingly used as it results in less thermal tissue damage with superior healing. However, tissue dissection with this device produces a dense cloud of cellular debris which may contain viable cells The aim of this study was to assess the viability of airborne cells released during cancer dissection using ultrasonic or electrical energy.

Flank tumours ($n = 8$) measuring 1 cm^3 were induced in WAG rats by subcutaneous injection of 2×10^6 CC531s colonic cancer cells Electrosurgery was performed using a high-frequency monopolar unit with a needle electrode at 60 W in cutting mode. Ultrasonic dissection was performed at maximum power output (tip excursion 80 μm at 55·5 kHz) in cutting mode. The smoke plume was aspirated with a vacuum pump and bubbled under Hank's balanced salt solution to trap any airborne cells. The viability of the cellular material was blindly assessed with the trypan blue test and by *in vitro* culture for 7 days The morphology of the cellular debris was studied by examination of cytospin preparations.

High concentrations of cellular debris were liberated during dissection with both devices However, no viable cells were isolated, nor did *in vitro* cell growth occur with either device. Examination of the debris from the ultrasonically activated scalpel demonstrated a characteristic mixture of amorphous forms and very few morphologically intact cells. The cauterized tumour produced charred cells and tissue fragments.

In conclusion, this study demonstrates the oncological safety of the ultrasonically activated scalpel Both electrical and ultrasonic energy release only non-viable airborne cells

Influence of display location on endoscopic task performance

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In endoscopic surgery, the display system is the visual interface between the surgeon and the operative field. The aim of the study was to investigate the influence of display location on task performance with regard to the surgeon and workstation.

The task was tying a surgeon's knot inside a trainer The monitor location was varied from (1) in front, (2) right and (3) left of the surgeon. At each location, the monitor planar direction was either vertical at the eye level (EL) of the surgeon or tilted towards the horizontal plane for gaze-down viewing at the same level as the workstation (WL) The distance between the monitor and the surgeon's eye was kept at 1 m. Three positions of the instruments were used to give different levels of task difficulty. Ten surgeons participated in the study and each performed 108 knots in a random sequence. Each knot was distracted with a tensiometer and a knot quality score (KQS) was obtained from analysis of the force–extension curves. The data were analysed with the Mann–Whitney *U* test and Kruskal–Wallis one-way analysis of variance.

The front monitor location had a shorter execution time (median 69 s) than lateral locations (median 78 and 77 s, $P < 0.0001$), with no significant difference in KQS With front monitor location, WL had a shorter execution time than EL (median 65 *versus* 72 s, $P < 0.01$) with no significant difference in KQS. The influence of monitor location was maintained for all levels of task difficulty.

Task performance improves when the monitor is placed in front of the surgeon coaxial with instrument direction and at the same level as the operative field, to allow gaze-down viewing by the surgeon.

Influence of two- and three-dimensional imaging systems on the performance of laparoscopic cholecystectomy

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In minimal access surgery (MAS), the surgeon has to reconstruct a three-dimensional (3-D) picture from a two-dimensional (2-D) image. The aim of this prospective randomized clinical trial was to investigate the influence of 2-D and 3-D imaging modalities on the performance of laparoscopic cholecystectomy (LC).

Sixty patients undergoing LC were randomized to imaging with a 2-D Storz system with a three-chip camera and a 3-D Zeiss system Operators were four senior registrars; each performed 20 LCs before entering the trial. The camera drivers were two consultants with an interest in MAS. Each LC was divided into four steps· (1) removal of adhesions to the gallbladder and dissection of the cystic pedicle, (2) cannulation of the cystic duct for cholangiography; (3) ligation of the cystic duct; and (4) resection of the gallbladder from the liver bed The degree of difficulty of LC was assessed by the consultant surgeon using a standard grading system (1–3). The execution time and errors encountered during the procedure were the endpoints of measurement. Data were collected by an independent research surgeon who did not take part in the study; they were analysed with the Mann–Whitney *U* test.

The two groups were matched for age, sex and degree of difficulty of the operation. The median execution time for steps 1–4 was 2100, 225, 182 and 610 s for the 2-D system and 1680, 230, 180 and 660 s for the 3-D system. Fifteen errors (eight with the 2-D and seven with the 3-D system) were encountered with hook diathermy to the gallbladder and liver, and one hole to the diaphragm (with the 3-D system), with no clinical consequences. There was no significant difference between the two systems in the execution time or error rate These results were also obtained for each step and at each degree of difficulty.

With the current technology there is no significant difference in the performance of laparoscopic cholecystectomy using 2-D or 3-D imaging systems.

Correlation between blood loss during liver resection and inferior vena cava pressure

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Historically, blood loss during liver resection has been extensive. In more recent times, sophisticated instrumentation and surgical techniques have decreased transfusion requirements. Blood transfusion is now regarded as one of the major determinants of mortality and morbidity in liver resection surgery. So how does inferior vena cava (IVC) pressure relate to blood loss during liver resection?

A study was conducted to monitor venous pressure within the retrohepatic part of the IVC during liver resection Results from 20 patients suggest that blood loss during liver resection is directly proportional to venous pressure within the IVC. It is observed that, when the caval pressure is less than 6 cmH$_2$O, the operating field is almost bloodless when the liver parenchyma is divided (mean blood loss 363 (range 305–465) ml). When the caval pressure is between 6 and 12 cmH$_2$O, the liver becomes congested and bleeding from the liver surface is significantly higher (mean blood loss 1259 (range 415–1789) ml). When caval pressure reaches above 13 cmH$_2$O, bleeding from the liver surface may be so brisk that the operation may have to be halted temporarily until the pressure has been lowered artificially (mean blood loss 2703 (range 2360–3450) ml). Correlation between IVC pressure and blood loss is strong ($r = 0{\cdot}93$, $P < 0{\cdot}001$)

It is also observed that there is a threshold pressure in the cava, which varies from patient to patient, below which the patient becomes unstable haemodynamically. This phenomenon is due to low venous return.

This study suggests that one of the keys to decreasing transfusion requirements during liver resection is to lower IVC pressure while respecting venous return.

Postprandial uncoupling of intestinal smooth muscle: is it related to insulin?

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After operation the intestinal response to meals is frequently altered. Previously this laboratory has shown that intestinal slow wave frequency (SWF; cycles per min) and slow wave propagation velocity (SWPV; cm s^{-1}) decreases in cats up to 3 h postprandially. The decrease in SWPV was attributed to uncoupling of intestinal muscle cells due to release of an uncoupling factor

The purpose of this study was to determine whether the postprandial release of insulin might contribute to this process

In six cats, eight pairs of serosal electrodes were implanted 4 cm apart on the jejunum, and an indwelling catheter was placed in an external jugular vein Myoelectrical activity was recorded after an 18-h fast. After 1 h of control recordings each cat was either fed 60 g canned cat food or injected with porcine insulin (0·05 units kg^{-1}) via a peripheral vein Recordings were continued for 3 h. Each cat was studied at least three times in each setting In all experiments serum glucose and insulin levels were measured during fasting and at 15 min, 1 h and 3 h after feeding or insulin injection.

The SWPV and SWF data are shown in the *Table*

	SWF (cycles per min)		SWPV (cm s^{-1})	
	Feeding	Insulin	Feeding	Insulin
Fasting	19·04(0·3)	19·12(0·2)	2·24(0·1)	2·43(0·1)
15 min	18·52(0·2)	18·52(0·2)	1·81(0·1)	1·72(0·1)*
1 h	18·46(0·2)	18·21(0·2)*	1·55(0·1)*	1·69(0·1)*
3 h	19·56(0·3)	18·59(0·3)	1·50(0·1)*	1·51(0·0)*

Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* control (fasting)

Plasma insulin levels following feeding and insulin injection were similar

In conclusion, intravenous injection of insulin to the plasma level that occurs postprandially mimics the postprandial decrease in SWPV and SWF.

Heparin, hydrocortisone and administration via the basilic vein reduce the incidence of thrombophlebitis during peripheral intravenous nutrition

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Peripheral vein thrombophlebitis (PVT) is a major obstacle to successful and prolonged administration of peripheral parenteral nutrition. Intravenous heparin and hydrocortisone and the application of a topical glyceryl trinitrate (GTN) patch are effective in reducing the incidence of PVT. The purpose of this study was to compare the effects of heparin and hydrocortisone added to the infusate with the topical application of a GTN patch, placed directly over the catheter tip, on the incidence of PVT during the administration of intravenous nutrition (IVN)

Some 72 patients were randomized to receive standard IVN (1200 osm kg^{-1}) administered through a fine-bore polyurethane catheter with heparin (1500 units) and hydrocortisone (15 mg) added to the infusate (control group, $n = 38$) or standard IVN with a 5-mg GTN patch applied to the skin directly overlying the catheter tip (study group, $n = 34$) Arms were examined daily and catheters removed if any signs of PVT became evident (pain, tenderness, erythema, palpable increase in temperature, swelling or a palpable venous cord) The two groups were matched for age, sex, indications for IVN and total number of days for which IVN was administered.

The time of onset of PVT was delayed in the control group compared with that in the study group ($P < 0{\cdot}05$) In addition, use of the basilic vein reduced the incidence of PVT when compared with the cephalic vein ($P < 0{\cdot}05$).

The results of this study suggest that peripheral vein IVN should be prescribed with the addition of heparin and hydrocortisone and administered via the basilic vein, whenever possible, in order to improve the efficacy of this route of administration and reduce complications associated with PVT.

Effect of laparoscopy on peritoneal fibrinolytic activity

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Intra-abdominal adhesions are a common source of morbidity following abdominal and pelvic surgery. Peritoneal fibrinolytic activity is mediated by a balance between tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI). Reports suggest that laparoscopic surgery results in fewer postoperative adhesions, but its effect on peritoneal fibrinolytic activity is not known. The effect of laparoscopy on peritoneal fibrinolytic responses was investigated.

Male Sprague-Dawley rats were divided into three groups: controls ($n = 4$), laparoscopy for 1 h ($n = 8$) and laparotomy for

1 h ($n = 8$). Laparotomy was achieved with a 5-cm midline incision. Laparoscopy was performed by carbon dioxide insufflation at 4 mmHg through a 0·5-cm port. Six hours and 4 days after operation the rats were killed and 6-mm punch biopsies of peritoneal tissue obtained. Peritoneal fibrinolytic activity was measured using the fibrin plate method and PAI activity was determined by a chromogenic substrate assay.

	Control	Open 6 h	Laparoscopy 6 h	Open day 4	Laparoscopy day 4
tPA (units cm^{-2}) × 10^{-3}	525(227)	265(98)*	289(109)*	1435(393)	1021(376)†
PAI (units ml^{-1})	7·5(6·6)	12·7(3·2)	17·2(10·0)	14·5(9·7)	12·3(5·2)

Values are mean(s.d.) *$P < 0·001$ *versus* control, †$P < 0·05$ *versus* laparotomy day 4 (one-way analysis of variance)

Surgery resulted in a biphasic fibrinolytic response with marked depression of tPA activity at 6 h accompanied by an early and sustained increase in PAI activity. Laparoscopy caused a significant reduction in the day 4 peak in tPA activity compared with open surgery. This attenuated fibrinolytic activity following laparoscopy may reflect reduced intra-abdominal trauma as the degree of peritoneal insult correlates with postoperative adhesion formation.

Novel explanation for the role of the dermis in controlling scar contraction

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Wound contraction and fibrosis are complications of deep dermal wound healing. Fibroblasts that take part in this process are derived from the subdermal tissue. However, the dermal fibroblasts are inactive; the reason for this is unknown. Previous studies have shown that citrate buffer extract from human dermis (extract D) can inhibit the ability of fibroblasts to produce contraction of collagen lattice *in vitro*. The aim of this study was to investigate the mechanism by which the human dermal extracts affect the behaviour of fibroblasts in hydrated collagen lattices (FHCLs) (artificial dermis).

Dermal extracts were prepared from the dermis of seven patients, each one in triplicate, by using successive solvents: water, normal saline, 1 mol l^{-1} saline, citrate buffer and urea. FHCLs (42 lattices) were prepared, including controls ($n = 21$); the rest were treated with dermal extract D. After measuring the amount of contraction, cell counts were carried out each day for 4 days. Flow cytometry techniques were used for studying the cell cycle after treatment with dermal extract D, in which the DNA was stained with propidium iodide, and chicken erythrocytes were used as a standard. The effect of extracts on fibroblast migration was examined through a fibronectin-coated polycarbonated filter (migration assay chamber).

Cell counts showed that extract D caused marked inhibition of fibroblast proliferation without any toxic effects on the cells, particularly on days 1 and 2. On day 1 (nine lattices) the cell proliferation index (PI) was + 1·08 and the area of contraction was 43 per cent of the initial area. On day 2 (three lattices) the PI was + 1·127 and the area of contraction was 55 per cent. In the control (untreated) lattices ($n = 9$), PI was + 1·198 and the area of contraction was 81 per cent on day 1; PI was + 1·31 and the area of contraction was 84 per cent by day 2 ($n = 3$). Cell cycle studies showed that most cells (60 per cent) remain at the S phase of the cell cycle and there was a significant S-phase block ($P < 0·01$, Student's t test). Migration assays showed that fibroblast migration was significantly reduced ($P < 0·05$).

Human dermis contains factor(s) that can inhibit the ability of fibroblasts to produce contraction. This effect may be due to inhibition of fibroblast proliferation and migration. The dermal factor(s) can be extracted by citrate buffer. These findings have important implications for minimizing scarring in patients with major burns.

Primary medical treatment of locally advanced breast cancer: recurrence and survival

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Patients with locally advanced breast cancer treated with surgery alone have a poor survival rate and a high local recurrence rate. Such patients have been treated with neoadjuvant chemotherapy, but with varying success and toxicity.

In the authors' unit 82 patients with T_3, T_4 and/or N_2 tumours were treated with up to six cycles of cyclophosphamide, vincristine, prednisolone and doxorubicin. Patients then received radiotherapy to the breast (4500 cGy) and to the lymph-draining areas (5000 cGy). Assessment of the response to chemotherapy and radiotherapy was made clinically and mammographically. Statistical analysis (Cox proportional hazard model) was carried out to determine predictors of survival.

The response rate after chemotherapy was 84 per cent (complete response (CR) 25 per cent, partial response (PR) 60 per cent). Following radiotherapy, this was increased to 87 per cent (CR 50 per cent; PR 37 per cent). The histological CR rate was 60 per cent. The probability of local control was 0·75 and that of survival at 5 years was 0·62 (median follow-up 54 months). Independent prognostic indicators for survival are shown in the *Table*.

	Range	b	Exp^b
Age (years)	33–81	− 0·0267	0·945 (0·94–1·00)†
Complete response after chemotherapy		− 0·8229	0·44 (0·24–0·79)
Local recurrence		0·0342	0·71 (0·50–1·00)*
Metastasis		− 0·6133	0·54 (0·31–0·95)*

Values in parentheses are 95 per cent confidence intervals. b, expression coefficient; exp^b, proportional hazard. *$P < 0·05$, †$P = 0·08$

Combination chemotherapy and radiotherapy achieved satisfactory local control in locally advanced breast cancer; independent predictors of survival in these patients have been identified.

Digitization improves mammographic assessment of response to chemotherapy in breast cancer

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The best method of assessing breast cancer response to chemotherapy has still to be established. Computer-assisted digital techniques may help in the interpretation of sequential mammograms and response to treatment.

Images were obtained from patients with breast cancer (T_2 (greater than 4 cm), T_3, T_4; N_2) treated with neoadjuvant chemotherapy. Mammography was performed at diagnosis and after completion of chemotherapy. Films were digitized on a LUMISCU 100 scanner at 400 μm resolution over an optical density range of 0–3·8. Each series of films was corrected for variations in exposure, compression of the breast and patient position. The optical density of the whole breast and of the tumour area was determined using the ANALYZE imaging software.

Some 40 patients (124 evaluated) who had a mammographically static response were identified. A decrease in density of greater than 10 per cent was considered significant. Of these, 17 had a decrease in the density of the tumours and 23 had no change. Of the 17 with a density decrease, 13 had a clinical response (complete or partial) and four had no clinical response; 11 had a good pathological response (minimal residual disease) and six a poor response. Of 23 patients with no density change, eight had a clinical response and 15 had no response; two had a good pathological response and 21 a poor response (*Table*).

	Density change ($n=17$)	No density change ($n=23$)
Clinical response	13	8
No clinical response	4	15
Good pathological response	11	2
Poor pathological response	6	21

Change in density is correlated to clinical ($P<0{\cdot}01$) and pathological ($P<0{\cdot}001$) response. Mammographic digitization can substantially improve the interpretation of serial mammograms in patients receiving chemotherapy for breast cancer.

Relationship between duration of tamoxifen therapy and endometrial thickness

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Tamoxifen has an agonist action on the endometrium which is associated with an increased risk of endometrial cancer, and screening for endometrial abnormalities by transvaginal (TV) ultrasonography of women treated with tamoxifen has been suggested.

Some 193 women receiving tamoxifen were screened by TV ultrasonography and endometrial thickness was measured. Length of time on tamoxifen ranged from 5 to 190 (mean 64) months and endometrial thickness from 1 to 38 (mean 7·8) mm. There was a statistically significant ($P=0{\cdot}0001$) positive correlation between length of time on tamoxifen and endometrial thickness.

In the first 100 of these women, outpatient hysteroscopy was attempted and was successful in 88 cases. Of these 88 patients, 48 had endometrium less than 5 mm and 40 had endometrium of 5 mm or more in thickness. On hysteroscopy 62 women had atrophic endometrium and 26 had benign features (none of them premalignant), so that there were 14 false-positive scans. From procedure scores, TV ultrasonography is better tolerated than hysteroscopy ($P<0{\cdot}001$).

There is a high (greater than 50 per cent) incidence of endometrial thickening in women taking tamoxifen, as assessed by TV ultrasonography. More than one-third of these patients did not have endometrial thickening on subsequent assessment. Length of time on tamoxifen relates to thickening. Although TV ultrasonography is well tolerated, it is not an ideal screening tool.

Immunization with cytokine-secreting tumour cells inhibits metastasis from breast cancer in a tumour-bearing animal

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The widespread use of cytokine gene therapy for cancer is limited by the difficulty in establishing cell lines from primary tumours for stable gene transfection. A novel gene delivery method was devised which produces transient transfection in primary human tumours. Experiments were performed to demonstrate its efficacy in generating tumour cell vaccines to inhibit metastasis in tumour-bearing hosts.

Inoculation of $2{\cdot}5\times10^4$ 4T1 breast cancer cells into the footpads of Balb/c mice leads to local tumour growth and the development of pulmonary metastases. Murine interferon (mIFN)γ-secreting 4T1 cells (4T1-pMP6A/mIFN) and control transduced 4T1 cells (4T1-pMP6A) were generated by lipofection using a cationic liposome complexed to a novel adeno-associated viral plasmid encoding the mIFN gene.

Unmodified 4T1 cells were inoculated into the footpads on day 1. Weekly subcutaneous vaccination with phosphate-buffered saline (PBS), 2×10^6 irradiated 4T1 cells, or bulk-transfected irradiated 4T1-pMP6A or 4T1-pMP6A/mIFN cells was commenced on day 7. Hindlimb amputation was performed at a footpad diameter of 6 mm (mean 28 days). Mice were killed 24 days after operation and metastatic disease was determined by weighing lungs at the time of harvest. Results are shown in the *Table*.

Vaccination group	Lung weight (mg)
PBS	920(75)
4T1	940(100)
4T1-pMP6A	965(90)
4T1-pMP6A/mIFN	530(110)

Values are mean(s.e.m.)

A significant reduction was seen in the pulmonary metastatic load of mice immunized with cytokine gene-modified tumour cells compared with that in mice given control immunizations ($P=0{\cdot}002$, Kruskal–Wallis test). These data suggest that use of bulk-transfected gene-modified tumour cell vaccines may provide a useful therapeutic option for treating patients with breast cancer.

Pretreatment levels of acute-phase proteins: independent indicators of survival in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy

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Serum albumin and C-reactive protein (CRP) levels have been suggested to be prognostic indicators in patients with cancer of the colon and pancreas. However, the value of acute-phase proteins in breast cancer remains unclear. It has also been shown that in patients with metastatic colorectal cancer pretreatment serum albumin levels are a predictor of subsequent response to chemoimmunotherapy.

The aim of this study, therefore, was to investigate the prognostic value of pretreatment levels of acute-phase proteins (albumin, CRP, α_1-antitrypsin and transferrin) in patients undergoing treatment with neoadjuvant chemotherapy.

Patients with locally advanced (T_3, T_4, N_2) breast cancer ($n=80$) were treated with six pulses of chemotherapy comprising doxorubicin (50 mg m^{-2}), cyclophosphamide (1 g m^{-2}), vincristine (1·5 mg m^{-2}) and prednisolone (40 mg per day for 5 days) at 21-day intervals. Using the Cox proportional hazard model, the prognostic value for survival of age, pretreatment albumin, CRP, α_1-antitrypsin and transferrin levels, clinical node status and tumour stage were examined (*Table*)

	Range	*b*	exp^b
Albumin	33–50 g l^{-1}	−1·20	3·00 (0·65–0·94)‡
CRP	1–65·5	0·29	1·34 (0·35–5·03)
α_1-Antitrypsin	0·86–2·42	0·34	1·42 (0·62–3·16)
Transferrin	1·41–3·61	−0·85	0·43 (0·19–0 97)†
Clinical node status*	0–1	−1·25	0·29 (0·11–0·75)†

Values in parentheses are 95 per cent confidence intervals. *1, nodes involved; 0, nodes not involved. *b*, expression coefficient; exp^b, proportional hazard. †$P < 0·05$, ‡$P < 0·01$

Pretreatment serum albumin and transferrin levels are independent prognostic indicators for survival in patients with locally advanced breast cancer receiving neoadjuvant chemotherapy.

Increased frequency of genetic alterations in the progression of proliferative breast disease to ductal carcinoma *in situ*

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The aim of this study was to reconstruct the molecular evolution of breast cancer progression with particular emphasis on the critical preinvasive steps. The authors have previously shown that ductal carcinoma *in situ* (DCIS) has chromosomal imbalances involving chromosomes 1, 3, 10, 17 and 18. Critical events must occur at an earlier stage than DCIS. Therefore, 31 cases of proliferative disease without atypia (PDWA) were analysed by fluorescence *in situ* hybridization using chromosome-specific centromeric probes for chromosomes 1, 3, 6, 10, 17 and 18.

Gains and losses of chromosomes were found that paralleled the findings in DCIS but at a reduced frequency, with the exception of chromosome 6 which showed no imbalance in DCIS or PDWA. In particular, there was a substantial increase in the frequency of chromosomal gains affecting chromosomes 3 and 17 (chromosome 3: DCIS 80 per cent, PDWA 6 per cent; chromosome 17. DCIS 78 per cent, PDWA 16 per cent). Detectable chromosomal imbalances were also found in chromosomes 1, 10 and 18 (chromosome 1: DCIS 14 per cent, PDWA 5 per cent; chromosome 10: DCIS 26 per cent, PDWA 11 per cent; chromosome 18: DCIS 28 per cent, PDWA 15 per cent).

It is concluded that: (1) chromosomal imbalances are detectable in PDWA and mirror those detected in DCIS, although at a lower frequency; (2) in comparing the two groups (PDWA and DCIS), critical genetic events affecting chromosomes 3 and 17 occur which may represent critical steps in the progression of preinvasive disease, and (3) these data are consistent with the hypothesis that PDWA can evolve to DCIS and that interphase cytogenetics may prove valuable in identifying subpopulations of PDWA that closely resemble DCIS at a molecular level and therefore have a greater risk of progression

Basic fibroblast growth factor infusion increases vascularity and blood flow of established tumours

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Poor vascularity limits chemotherapy uptake into solid tumours. The authors have previously shown that *in vivo* growth of an experimental tumour in the presence of basic fibroblast growth factor (bFGF) increases tumour vascularity and blood flow. This study was designed to assess whether administration of bFGF to established tumours increases vascularity or blood flow.

Some 10^6 hooded sarcoma-N (HSN) cells were injected subcutaneously into Chester Beatty hooded rats. After 10 days' growth the tumours were infused directly with bFGF or saline (controls) for 14 days using an osmotic minipump. [^{125}I]iodoantipyrine ([^{125}I]IAP) was then infused for 30 s and the animals were killed.

Tumour vascularity was demonstrated by OX43 immunohistochemical staining. Vessel count was determined at ×400 magnification by graticule counting. Blood flow was determined by the autoradiographic ratio of [^{125}I]IAP activity between the edge and within the tumour.

	No. of rats	Vascularity (mm m^{-3})*	*P*	Blood flow (tumour : edge ratio)*	*P*
2 mm from edge into tumour					
Saline	6	11(8)	0·05	0·66(0 49)	0·003
bFGF	5	93(87)		2·10(1·23)	
Tumour centre					
Saline	6	0(0)	0 1	0·03(0·01)	0·006
bFGF	5	8(9)		0·30(0 13)	

*Values are mean(s.d)

bFGF infusion into established HSN tumours increased tumour vascularity and blood flow. This approach may improve chemotherapy uptake into established solid tumours.

Ezrin is a novel motility and invasion suppressor molecule in human cancer cells

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Ezrin is a membrane cytoskeleton linker protein and may play a role in the membrane ruffling and motility of cells. This study sought to determine the role of this molecule in the motile and invasive nature of colonic cancer cells.

Human colonic cancer cells HT115 and HRT18 were used. Ezrin was determined by immunofluorescent staining and Western blotting. Cell motility, morphology and invasion were determined by colloidal gold phagokinetic tracking, scanning and transmission electron microscopy (EM), and Matrigel invasion assays respectively. Cell–cell adhesion was assessed with a cell–cell aggregation assay and membrane ruffling by means of time-lapse video recording. Both cells expressed ezrin strongly in the cytoplasm and in intercellular junctions. Removal of the ezrin molecule was facilitated by an antisense knock-out technique using a specific ezrin antisense oligonucleotide (oligo). This resulted in complete loss of cellular ezrin. Ezrin-negative cells showed a marked difference in the following parameters compared with controls. The *Table* shows HT115 cells.

	Control	Oligo treated	*P*
Aggregation index	0·5(0·12)	0·02(0 2)	<0·05
Invasion index	1 6(0·09)	15·2(3·4)	<0·01
Ruffling index	1·75(0·13)	0·76(0·12)	<0·01

Values are mean(s.d.)

HRT18 cells showed a similar response to HT115. Antisense-treated cells showed a marked reduction of cell–cell adhesion and an increase in *in vitro* invasion. The treated cells also revealed a marked increase in cell motility and spreading as shown by phagokinetic assays and scanning EM. Transmission EM also revealed an increase in cell–cell dissociation.

It is concluded that ezrin acts as a motility and invasion suppressor molecule, partly as a result of its involvement in cell–cell adhesion mechanisms. Such a molecule may be important in the control of invasion and metastasis in colonic cancer

Telomerase activity in desmoids

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Desmoids are poorly understood fibromatous proliferations that occur particularly in association with familial adenomatous polyposis (FAP) and are an important source of mortality and morbidity in patients with FAP. Telomerase may be required for unlimited growth of cells; its activity is repressed in most human somatic tissues, but is detectable in immortal cell lines, germ cells, many malignancies and some benign lesions. The levels of telomerase activity were assayed in desmoids from patients with and without FAP to assess the role of telomerase in the development of these lesions, and its potential as a prognostic marker and possible target for treatment.

Protein extracts from 11 desmoids from nine patients with FAP and ten desmoids from ten patients without FAP were analysed for telomerase activity by the telomeric repeat amplification protocol, a sensitive polymerase chain reaction-based assay. Six fibrosarcomas and a fibrosarcoma cell line were used as positive controls; all displayed telomerase activity.

No telomerase activity was detected in any of the 19 desmoids studied.

In conclusion, there is evidence of the lifting of telomerase repression in some regenerative lesions and benign tumours (including breast fibroadenoma and colorectal adenoma) as well as in frank malignancy. The absence of this in desmoids, increasingly thought to be neoplasms associated with *APC* gene mutation, is surprising. The lack of telomerase activity in desmoids gives no further insight into their pathogenesis, other than to suggest that mechanisms other than reactivation of telomerase activity may operate in these proliferative neoplasms, and does not offer the biochemical marker or possible target for treatment by telomerase inhibition that is the subject of so much interest currently.

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Correspondence

Percutaneous transluminal angioplasty of the internal carotid artery

Sir

We read the Leader from St Thomas' Hospital (*Br J Surg* 1996; 83: 1171–3). The endovascular management of symptomatic internal carotid artery disease is a rapidly evolving technique receiving considerable attention within the literature and scientific community

(1) We are unsure of the value of comparing the length of inpatient stay following carotid endarterectomy with the length of time required to perform a carotid angioplasty. Although the length of stay after endarterectomy has fallen in recent years, those undergoing angioplasty may require an overnight stay and the mean length of time to perform a carotid angioplasty in this country[1] is between 45 min and 1 h.

(2) The main concern of carotid angioplasty is not cerebral embolization but to avoid significant morbidity and mortality from the procedure. Cerebral embolization may well be one of the mechanisms that cause significant morbidity but clinical cerebral deficits do not necessarily follow embolization. Clearly more work is required on the physiological effects of microembolization.

(3) Flow interruption in the internal carotid artery, when cerebral protection is not used, occurs for only 15 s (the length of time the balloon is inflated) and is certainly not analogous to the traditional balloon occlusion test.

(4) Throughout the article the authors choose to quote the worse case scenario from the reviewed papers. Included within this is the suggestion that failure to pass the guidewire is a complication. This is a technical failure not a complication. A failure rate of 32 per cent is given but in contemporary practice this occurs in approximately 2 per cent[2].

(5) The authors suggest that the presence of pain during dilatation is a complication. The pain following angioplasty lasts 15 s and the authors fail to mention the discomfort caused by the neck incision following carotid endarterectomy as well as the risk of cranial nerve injury.

(6) Transient bradycardia and hypertension during inflation of the balloon certainly occurs during carotid angioplasty. In our randomized work, the hypertension was more profound and longer lasting following carotid endarterectomy than following angioplasty[3].

(7) The authors describe complications that they would expect to see (false aneurysm formation, limb embolization, haemorrhage) rather than what has been reported.

Internal carotid artery angioplasty is a new and developing technique that should be evaluated under strict conditions. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), which randomizes symptomatic patients with high-grade carotid stenoses between surgery and endovascular techniques, will go some way to providing reliable data and I am sure that the authors will be aware that there are large randomized trials in preparation that should start in 1997. It is certain that we will not have to wait the 40 years that occurred between the development of carotid endarterectomy and its scientific justification.

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Authors' reply

Sir

Thank you for allowing us to reply to the letter from Mr Gaines *et al.*

(1) We did not attempt to compare inpatient stay after carotid endarterectomy with time to perform angioplasty. The article stated that one of the perceived benefits of angioplasty over endarterectomy was decreased procedure time and inpatient stay. We quoted a mean carotid angioplasty procedure time and we quoted our usual inpatient stay following carotid endarterectomy.

(2) The article attempted to include all causes of morbidity and mortality following carotid angioplasty. We pointed out that cerebral embolism is common and usually symptomless, but we are still concerned that this may be important. The long-term effects of emboli on cognition and other cerebral functions are not known.

(3) Although practices in many centres may have changed, longer balloon inflation times have been used in the past, as have multiple dilatations. Many radiologists have now reduced carotid balloon inflation time to 10–15 s because of anxieties regarding obliteration of cerebral blood flow for longer periods. This is shorter than the inflation times used in other arteries with comparable stenoses. In other arteries 15 s is often not a sufficient inflation time; this may explain the apparent high rate of restenosis following carotid angioplasty. We did not include in the Leader mention of the use of vascular stents as this was not in the remit.

(4) We agree that technical failure of a procedure is not a true 'complication' – unless you are the patient. A wide range of technical failure rates is reported, the higher failure rates being associated with greater degrees of stenosis.

(5, 6) Pain and hypotension are well recognized complications of carotid angioplasty

(7) We have listed complications that are known to have occurred, but have not yet been reported.

We agree that this new technique should be carefully evaluated and consider it is important to highlight potential problems. We do not believe that anyone should start using this procedure until the results of the CAVATAS have been reported. Anxieties will continue even after this study because of its selective admission policy.

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Laparoscopic appendicectomy

Sir

In attempting to define the role of diagnostic laparoscopy in the management of patients with suspected acute appendicitis, Mr Tate (*Br J Surg* 1996; 83: 1169–70) overlooked an important third approach. To undertake laparoscopy 'on all patients admitted to hospital with acute abdominal pain', which is the first approach suggested in the article, is both expensive and an unnecessary risk to a proportion of patients. The other approach goes to the other extreme by suggesting 'laparoscopy after the clinical diagnosis of appendicitis has been made and the decision already taken to operate'. We contend that diagnostic laparoscopy has its most useful role when there is persisting diagnostic uncertainty

Rather than replacing 'an expectant approach' it proves more useful if employed in conjunction with 'a period of active observation' which has itself been shown to improve diagnostic accuracy[1]

It is true that laparoscopic appendicectomy provides an excellent opportunity for surgical trainees to acquire basic laparoscopic skills. The provision of experienced supervision for those traversing the learning curve remains one of the most important challenges facing those who seek to provide for the ongoing development of safe laparoscopic surgery.

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1 Jones PF. Practicalities in the management of the acute abdomen. *Br J Surg* 1990, 77· 365–7.

Prospective randomized trial comparing sequential avulsion with stripping of the long saphenous vein

Sir

Mr Blair and colleagues have highlighted that sequential avulsion of the long saphenous vein (*Br J Surg* 1996; 83: 1559–62) results in less pain and bruising when compared with removal with a stripper. A better cosmetic outcome is unlikely with this approach. This technique is likely to generate a shorter length of scar below the knee but it does leave 4–7 (median 5) scars in the thigh. In obese individuals it sometimes becomes difficult to palpate the taut length of vein distally in the thigh, and delivering the vein at these points can occasionally leave significant scars. As bruising is only a transient phenomenon, is the extent of bruising to be considered more important than the number of long-lasting scars, however small they might be? Perhaps an assessment of patient satisfaction regarding the cosmetic outcome might answer this question If the authors have any data on this, I would be very interested to know their results.

Return to work is an important endpoint of varicose vein surgery. From the data presented in the paper I could not detect any significant difference in activity or return to work between the two techniques.

Two methods were described to avoid the unsightly scar below the knee (cryostripping and pin-stripping). Another method is in wide use in the UK After dissection in the groin, a stripper wire is passed from the groin down the long saphenous vein. Before this, a long, strong tie is placed around the stripper head. The end of the stripper is extracted just below the knee through an incision of only 2–3 mm in length. The vein is then stripped to this incision, the vein alone removed through the stab incision over the stripper wire and the stripper then recovered back in the groin by pulling on the attached tie, thus delivering its head in the groin.

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Author's reply

Sir

There are many ways to remove the long saphenous vein in the thigh and Mr Sudhindran describes a variation of pin-stripping. This has not been subjected to a prospective randomized trial and a number of statements about sequential avulsion are misleading. It is true that sometimes in obese patients it is not possible easily to palpate the taut vein in the thigh. In this prospective randomized trial, however, in five of 40 patients randomized to stripping the stripper would not pass, and in only two patients randomized to sequential avulsion was it not possible to remove the whole length of vein in the thigh.

Others may judge whether a 2-cm cut below the hem-line is preferable cosmetically to the tiny scars made with modern avulsions. It is quite clear that sequential avulsion is a much less painful operation and this was reflected in the activity of patients: 13 of 40 patients who had undergone stripping were unable to climb stairs the day after surgery compared with only six of 40 who had had avulsion. This may also be an important point in determining the procedure to be adopted for day cases Personally, I believe that patients want a less painful operation with an improved cosmetic result.

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Audit of general practitioner referrals to a surgical assessment unit: new methods to improve the efficiency of the acute surgical service

Sir

The paper by Mr Dookeran and colleagues (*Br J Surg* 1996; 83: 1544–7) clearly shows that the provision of even a moderately experienced surgical opinion can reduce significantly the emergency admission rate from general practitioners. In our hospital, recent experience with a medical admissions unit has demonstrated a similar trend. As long as there appears to be cost savings, cash-strapped Trust managers will no doubt press for this sort of exercise to become more widespread. What the authors fail to explain in their paper, however, is the fate of the substantial number of patients complaining of abdominal pain who had 'no surgical problem'. Surely, if one is to make emergency admission to a surgical bed less accessible then one needs to know the effect on patients turned away as well as the detailed cost saving to the Trust accountants?

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Author's reply

Sir

Mr Wilkins' first question relates to follow-up and outcome analysis. Following completion of this study, a detailed audit of outcome for all patients evaluated in the surgical assessment unit (SAU) during the study period was attempted This consisted of a questionnaire sent to all general practitioners (GPs) in the area who were likely to have used the SAU. Despite reminders, responses were obtained from only 41 (45 per cent) of 92 GPs questioned. However, 92 per cent of respondents thought that patients seen in the SAU had an adequate clinical evaluation The outcome audit did not specifically inquire about the fate of patients who initially complained of abdominal pain and who were subsequently found to have no surgical problem when evaluated in the SAU. There were no complaints of adverse outcome for all patients discharged from the SAU both during and after the study period. We did not readmit any patients from the subgroup in question for further abdominal complaints, nor do we have knowledge that such patients were readmitted to neighbouring hospitals. The second question relates to cost analysis. Given our limited resources we could not structure our study differently. The ideal would be to randomize patients prospectively to both old and new types of admission system simultaneously, and then to perform diligent follow-up on all patients. Such a venture was clearly not a realistic proposition. The details of cost savings in this study at our hospital are clearly set out in the paper; however, savings anticipated at other hospital Trusts may vary depending on local conditions and structure of the acute surgical services. Consultants and Trust accountants should note that, although a significant number of urgent GP referrals may be inappropriate, this figure may vary substantially from region to region.

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Rectus sheath bupivacaine analgesia after aortic surgery

Sir

We were interested to read the Surgical Workshop by Mr Curley and colleagues (*Br J Surg* 1996; 83: 1558). In 1989, before laparoscopic cholecystectomy became fashionable, we described a similar technique for perfusion of transverse abdominal wounds with bupivacaine afer 'open' cholecystectomy[1].

Like Mr Curley and colleagues, we found no increase in wound infection in patients undergoing wound perfusion with bupivacaine or saline, and we were able objectively to demonstrate the analgesic effects of the technique using linear analogue pain scores and changes in demands with a patient-controlled analgesic device.

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Desmoids in familial adenomatous polyposis

Sir

Following your recent publication of the interesting review (*Br J Surg* 1996; 83: 1494–1504), we have operated on two patients with 'acute abdomens' caused by desmoid tumours in the small bowel mesentery. As emergency presentation of abdominal fibromatosis is not mentioned in the article, we would like to bring it to the attention of your readers.

A 33-year-old man presented with generalized peritonitis and gave a history of having noted an abdominal mass for 2 weeks. Due to abdominal muscle rigidity no mass was palpable on admission. At laparotomy peritonitis and a 12-cm tumour in the proximal small bowel mesentery were found. A hole on the left side of the hard tumour allowed insertion of an index finger into the necrotic centre, thereby revealing the source of the peritonitis Only 2 cm of superior mesenteric artery could be palpated between the pancreas and the inferior aspect of the tumour, and the transverse mesocolon and middle colic artery was inseparable from the mass. A biopsy and peritoneal lavage were carried out. The patient made an uneventful recovery and histology revealed abdominal fibromatosis. He is currently being assessed by computed tomography and angiography to plan further medical and/or surgical treatment.

A 67-year-old man presented with acute abdominal pain and cardiovascular collapse that responded to fluid resuscitation. Ultrasonography revealed an intact aorta but free fluid in the peritoneal cavity. At laparotomy a 3-litre haemoperitoneum was found with an 8-cm tumour in the middle of the small bowel mesentery. A hole in the right side of the tumour led to a central cavity filled with clot. There was no other source of bleeding. Wedge resection of the tumour included the overlying 70 cm of jejunum. The patient required a blood transfusion of 12 units of packed cells and 48 h of ventilation in the intensive care unit, but thereafter made an uneventful recovery. Histological examination revealed completely excised abdominal fibromatosis.

In addition to peritonitis and intra-abdominal bleeding, central necrosis of desmoid tumours in the small bowel mesentery can lead to the formation of an inflammatory mass or abscess, or enteric fistulae[1]. Bowel obstruction and torsion of a pedunculated tumour are other rare causes of an acute abdomen in patients with abdominal fibromatosis[2]. Whereas elective resection of uncomplicated mesenteric desmoids is not usually advised, in some emergency presentations, as in one patient described here, complete excision is mandatory.

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1 Maldjian C, Mitty H, Garten A, Forman W. Abscess formation in desmoid tumours of Gardner's syndrome and percutaneous drainage: a report of three cases. *Cardiovasc Intervent Radiol* 1995; 18: 168–71.

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Prospective randomized trial comparing postoperative pain and return to physical activity after transabdominal preperitoneal, total preperitoneal or Shouldice technique for inguinal hernia repair

Sir

We read with interest the prospective trial by Dr Schrenk and colleagues (*Br J Surg* 1996; 83: 1563–6) comparing the outcome of laparoscopic and Shouldice techniques for inguinal hernia repair The authors showed that laparoscopic (transabdominal preperitoneal (TAPP) or total preperitoneal) management of unilateral inguinal hernia does not offer significant advantages over the Shouldice repair concerning postoperative pain and return to physical activity. Such conclusions are different from those in a Swiss multicentre prospective trial[1], in which TAPP repair was associated with less pain and allowed earlier resumption of physical activity. In a recent review[2] of multicentre trials published since 1994 it was apparent that laparoscopic and open repair gave similar results, the only exception being increased costs and decreased time to return to work for laparoscopic repair. The conclusions reached by Dr Schrenk and colleagues are therefore particularly interesting, and confirm the fact that 'the return to physical activity and to work' is a difficult parameter to evalute

The point for discussion is different: the authors affirm that 'new methods for hernia repair must be more effective than standard techniques'. Can the Shouldice repair be considered a standard technique? The answer is probably yes if we consider its worldwide usage, but there are other techniques (tension-free repair, such as Lichtenstein's, Gilbert's and Rutkow's techniques), whose use is increasing. It may be more correct to compare laparoscopic repair with these techniques because they both require the placement of a prosthesis and are, therefore, tension-free repairs. Such comparison seems to favour the open repair, because of its low costs (day surgery), low morbidity rates, good patient compliance (minimal postoperative discomfort and recurrence rates of less than 1 per cent), and a similar time for complete recuperation[3,4]. We, therefore, suggest that future comparative trials should take into account laparoscopic *versus* tension-free open repair.

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1 Tschudi J, Wagner M, Klaiber Ch *et al.* Controlled multicenter trial of laparoscopic transabdominal preperitoneal hernioplasty *vs* Shouldice herniorraphy. Early results. *Surg Endosc* 1996; 10: 845–7.
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Successful use of size-mismatched liver allografts in children by delayed primary closure of abdominal wall

Sir

Delayed primary closure of the abdominal wall, as reported by Mr Soin and colleagues (*Br J Surg* 1996; 83: 1530–1), in the context of paediatric liver transplantation, was described by Schuster[1] for the management of giant omphaloceles in newborns. The technique includes suturing the abdominal wall muscles to the open weave of the polypropylene mesh, which is then incorporated into the healing tissues and does not separate from the wound edge. This property makes it a very suitable prosthesis across an open abdominal wound, encouraging the anterior abdominal wall muscles to stretch and so achieving tissue closure with staged reduction of the mesh over a period of several days or weeks. This technique is not possible with a Silastic silo, which will separate from the wound edge after 10 days.

The authors comment that 'granulation tissue grew into the mesh causing vascular adhesions of the mesh to the underlying liver and bowel loops' This leads to a delicate and potentially bloody dissection of the mesh when it is reduced. This can be avoided by placing a thin sheet of non-reactive material between the mesh and the abdominal organs. Silastic sheeting 0·01 mm thick is ideal for this purpose and need not be sutured in place as it is not providing support for the abdominal wall. As granulation tissue will not grow into Silastic sheeting, it can be removed easily at the time of final wound closure.

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1 Schuster SR. A new method for the staged repair of large omphaloceles. *Surg Gynecol Obstet* 1967, 125: 837–45.

Percutaneous transluminal angioplasty of the internal carotid artery

Sir

McGuinness and Burnand drew attention to the development of percutaneous transluminal angioplasty as an alternative to surgery for the treatment of internal carotid artery stenosis in a recent editorial (*Br J Surg* 1996; 83: 1171–3) We entirely agree that carotid angioplasty is an experimental procedure that should be carried out only as part of a randomized trial in centres with appropriate expertise, but the authors have overemphasized the minor morbidity associated with carotid angioplasty. They suggest that a disadvantage of angioplasty is that 'problems of cerebral ischaemia may be anticipated in patients with a discontinuous circle of Willis because the carotid blood flow is completely obstructed during balloon angioplasty' In fact, this situation provides one of the advantages of carotid angioplasty compared with carotid surgery. The duration of balloon inflation and carotid occlusion during angioplasty is actually shorter than occlusion times during carotid endarterectomy, even when shunts are used. For example, we have monitored the middle cerebral artery blood flow using transcranial Doppler ultrasonography in 12 carotid endarterectomies in which shunts were used. The mean time taken from clamping the common carotid artery to shunt insertion was 2 min 52 s and the time from shunt removal to the restoration of flow was 3 min 16 s. In nine of the 12 patients the middle cerebral artery velocity was reduced to half of its preclamped value. In contrast, the mean time for which middle cerebral artery velocity fell in 15 patients monitored during carotid angioplasty was 58 s, the balloon being inflated for a mean of 19·2 s. The ischaemic time during carotid angioplasty is therefore less during carotid endarterectomy.

The authors emphasize the frequency of complications of balloon angioplasty. With increasing experience, we have found that failure to manipulate the guidewire past the stenosis occurs in less than 10 per cent of patients and most of these undergo carotid endarterectomy. Arterial dissection following incorrect placement of the wire is certainly a potential hazard but appropriate choice of techniques and careful imaging during the procedure should minimize the incidence. Cervical pain used to be a common complication when balloons were of a diameter larger than the carotid artery. This is hardly ever a problem now as smaller balloons are used and the inflation pressure is monitored. Transient bradycardia and hypotension are caused by distortion of carotid baro-receptors and are avoided by the use of intravenous atropine before balloon inflation False aneurysms and embolic complications affecting the limb after femoral artery catheterization are uncommon.

We agree that restenosis may prove to be a disadvantage of carotid angioplasty but, to date, the long-term results in most patients are fairly durable. As with carotid endarterectomy, restenosis does occur but is rarely symptomatic It is not until carotid arteries become more than 80 per cent stenosed that there is a significant risk of recurrent symptoms. The pathology of restenosis after angioplasty, which results from smooth fibrous neointimal hyperplasia, may render restenotic lesions at lower risk of embolization than original atherosclerotic stenosis.

The main potential disadvantage of carotid angioplasty remains the risk of embolic stroke and carotid occlusion resulting from the procedure, just as this is the main risk of carotid surgery. Only randomized comparison between carotid surgery and angioplasty can determine how these two procedures compare. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) is the only ongoing randomized trial. The study now has 20 centres in the UK, Europe and North America. Our Monitoring Committee reported in November 1996, after analysing the data on over 300 patients, that there was no reason to stop the trial. We therefore plan to continue randomizing and will be carrying out an analysis with a minimum of 6 months' follow-up in 400 patients in October 1997. We hope that when we have the data available we will be able to answer some of the unanswered questions posed by McGuinness and Burnand.

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Randomized trial of periportal peritoneal bupivacaine for pain relief after laparoscopic cholecystectomy

Sir

In their randomized trial of bupivacaine for pain relief after laparoscopic cholecystectomy (*Br J Surg* 1996; 83: 1223–5) Mr Alexander and colleagues compared two regimens, both of which ignore the possibility of pain being in the muscle layer that was not injected; anyone who has ever tried to do a muscle biopsy under local anaesthetic will know that skeletal muscle is highly pain sensitive.

The second obvious weakness in their trial was that the bupivacaine was not infiltrated until after the ports had been inserted. Our neurophysiological colleagues suggest that the pain gate is ideally best closed before the stimulus is applied. It may well be that if the deep injection group had been given an entry puncture through all layers of the peritoneum they may have had better postoperative pain relief, and the trial may well have given a more conclusive answer.

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Author's reply

Sir

We appreciate the discomfort associated with muscle biopsy but the ports separate, rather than destroy, muscle and it is also unlikely that the combination of periperitoneal and subcutaneous injection fails to anaesthetize the muscle layer.

We are, of course, aware of pre-emptive analgesia and, while it is easy to inject the skin sites of trocar insertion, it is not so easy to predict the site of entry at the level of the peritoneum We have found our technique renders patients largely pain free a very short time after surgery.

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Incidence and nature of bile duct injuries following laparoscopic cholecystectomy: an audit of 5913 cases

Sir

We enjoyed reading the audit of laparoscopic cholecystectomy and bile duct injury from the West of Scotland group (*Br J Surg* 1996; 83: 1356–60) and were impressed with their classification of major and minor bile duct injuries. We were surprised by the scant reference given to the role of intraoperative cholangiography in the prevention of these injuries. It was stated that only 8·8 per cent of all procedures used imaging in a group where 'cholangiography was performed on a selective basis by most'. We would like to ask why, if a selective policy was adopted by most surgeons, the actual numbers of cholangiograms performed was so low. This is particularly surprising when intraoperative imaging of one form or another is increasingly being advocated on a routine basis[1].

The authors state that 'the majority of injuries were secondary to misidentification of anatomy' and go on to advocate several techniques to avoid injury, but fail to mention any form of imaging of the bile duct system during operation. Kullman *et al.*[2] published results last year showing how valuable intraoperative cholangiography is in diagnosing anomalous anatomy.

Intraoperative cholangiography prevents bile duct injury, certainly the most serious injury of bile duct resection, and with practice it is an easy, safe and quick procedure to perform. Bile duct injury is more common in the early part of a learning curve and we would therefore suggest that it is particularly at this time that surgeons should be taught to perform intraoperative cholangiography routinely

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1 Rothlin MA, Schob O, Schlumpf R, Largiadèr. Laparoscopic ultrasonography during cholecystectomy. *Br J Surg* 1996; 83: 1512–16.
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Author's reply

Sir

Mr Torkington and colleagues are concerned by our scant reference to the role of operative cholangiography in preventing bile duct injury during laparoscopic cholecystectomy. This issue had been discussed in our initial paper on this subject (Reference 27) and we wished to avoid repetitious debate on this controversial subject, particularly as the bile duct injury rate is now at levels comparable to those of the open procedure.

In patients awaiting cholecystectomy who have suspected bile duct stones, preoperative endoscopic retrograde cholangiopancreatography (ERCP) has become the procedure of choice and 14 per cent of the patients in this study had this performed. We are sure that this explains the low incidence of intraoperative cholangiography during laparoscopic surgery.

We agree in principle that increased use of intraoperative cholangiography, particularly if the anatomy is in any way unclear, may be helpful in decreasing bile duct injury during laparoscopic cholecystectomy. In the present study, however, four patients who had bile duct injury actually had intraoperative cholangiography; in two of these major bile duct trauma (division of common bile duct or common hepatic duct) had already occurred before imaging. In another patient the cholangiogram was misinterpreted and the bile duct transection detected only after operation. In the final patient bile duct injury occurred after demonstration of a normal operative cholangiogram during clipping of the cystic duct.

Bile duct injury during laparoscopic cholecystectomy is not completely avoided by operative cholangiography. Its more frequent use with meticulous dissection and clear demonstration of the biliary anatomy may lead to a further decrease in this complication.

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Colonic pouches in the treatment of low rectal cancer

Sir
I read with interest the Leading Article by Mr Seow-Choen (*Br J Surg* 1996, 83: 881–2) and add two comments.

The reasons proposed by Mr Seow-Choen for treating most cases of low rectal cancer with a colonic pouch–anal anastomosis (the need for total mesorectal and total rectal excision) are attractive. None the less, the contention that colonic pouches should be used routinely may be an overkill from the functional point of view. No doubt, colonic pouches result generally in better clinical function than a straight coloanal anastomosis, especially in the early months However, function is not better and may be inferior to a standard low anterior resection, both in terms of frequency and possible evacuation problems. It remains to be seen whether the possibly lower leakage rate following a colonic pouch–anal anastomosis[1,2], when compared with a straight anastomosis, really justifies converting a number of low anterior resections to pouch–anal anastomosis.

Second, evacuation problems can occur after construction of colonic pouches[3] and are usually due to pouch design. Fundamental to pouch design is the understanding of pouch evacuation dynamics. Pelvic pouches are largely non-motile, depending on mass colonic movements for initiation of defaecation, and helped by the increase in intra-abdominal pressure created by voluntary straining. The ease of evacuation is largely governed by how vertically a pouch lies in the pelvis, to utilize these forces. Investigating colonic pouch evacuation using defaecating proctography we found that one of the most important factors affecting postoperative function (in particular evacuation) was its lie in the pelvis (how obtuse was the pouch–anal angle)[4]. The construction of the pouch to lie as vertically as possible in the pelvis (by a combination of using short colonic lengths and anastomosing the pouch to the top of the anal canal) results in better function. Larger pouches, and pouches not wedged deeply in the pelvis so as to lie vertically, tend to accumulate faecal matter and eventually angulate forwards, impairing evacuation. Colonic pouches are effective but it is probably better to restrict their construction to patients in whom resection mandates a coloanal anastomosis.

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Egypt

1 Hallbook O, Pahlman L, Krog M, Wexner SD, Sjodahl R. Randomized comparison of straight and colonic J-pouch anastomosis after low anterior resection. *Ann Surg* 1996; **224**: 58–65.
2 Hallbõok O, Johansson K, Sjödahl R. Laser Doppler blood flow measurement in rectal resection for carcinoma – comparison between straight and colonic J pouch *Br J Surg* 1996, **83**· 389–92.
3 Berger A, Tiret E, Parc R *et al.* Excision of the rectum with colonic J pouch–anal anastomosis for adenocarcinoma of the low and mid rectum. *World J Surg* 1991; **16**. 470–7
4 Williams NS. Sphincter saving resection and total reconstruction for low rectal cancer. In: Williams NS, ed. *Colorectal Cancer.* London: Churchill Livingstone, 1996. 80.

Author's reply

Sir
I would like to thank Professor Marzouk for his interest and I am thankful for the opportunity to repeat the reasons for the routine construction of a colonic pouch for low rectal cancer as our views are essentially similar.

Total mesorectal excision is essential if a low pelvic recurrence rate is to be achieved following surgery for low rectal cancer. The entire rectum is best removed as any remnant will be ischaemic if total mesorectal excision has been performed. A colonic pouch construction will definitely improve neorectal function over that obtained with a straight coloanal anastomosis in such a situation. I have no doubt that colorectal anastomosis, that is, a low anterior resection, will have superior function to a colonic pouch but will be possible only if total mesorectal excision was not performed and the distal rectal stump is still viable. A low anterior resection should be performed only for tumours about 10 cm or more from the anal verge. Any patient with rectal cancer that is digitally palpable per rectum should have total rectal resection and total mesorectal excision for good oncological clearance.

I have stressed the use of a short pouch (7–8 cm) as well as the exclusion of the sigmoid colon if evacuatory problems are to be avoided following construction of a colonic pouch Furthermore, the colonic pouch must always be anastomosed to the top of the anal canal and not to any remnant of the lower rectum for two reasons pouch-to-rectum anastomosis results in evacuation problems and if total mesorectal excision occurred the ischaemic rectal remnant results in an ischaemic stricture or anastomotic leak with poor function. Using these principles, we have not had any patient with evacuation problems following colonic pouch surgery.

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British Journal of Surgery 1997, 84, 732–733

Book reviews

Causes and Control of Colorectal Cancer: A Model for Cancer Prevention

G. Kune. 240 × 160mm. Pp. 375. Illustrated. 1996. Boston, Massachusetts: Kluwer Academic Publishers. Price not supplied.

This book should be of great topical interest and its publication is timely as it reviews the aetiology, prevention and control of colorectal cancer (CRC) is a truly multidisciplinary fashion. The author is to be congratulated on producing such a compact, complete and readable book on a subject that continues to vex the efforts of many of us who are involved in the management of patients with this disease.

The first part of the book conveniently addresses the aetiology of CRC and covers a variety of factors, such as genetic and hereditary, diet, alcohol consumption, smoking and physical activity, to name but a few (there is even a chapter on the aetiological and epidemiological importance of religion and religiousness). Chapters are devoted to each of these subjects and the literature has been extensively researched. In the second part of the book special emphasis is placed on the prevention and control of CRC. It begins with a chapter on the general principles of cancer control and moves on to consider those methods which are applicable to CRC. Of particular importance and relevance to clinicians are the descriptions of CRC screening and methods of surveillance after potentially curative excision of a primary tumour The real strength of this book lies in its completeness in the discussion of a disease of multifactorial aetiology and the extensive referencing that has been undertaken. My only criticism relates to formatting errors during publication which have resulted in the reproduction of Chapter 5 in supplementary booklet form. Be this as it may, I consider this book essential for all those who are involved with the investigation into the causes of CRC and the practical management of patients with this disease

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Textbook of Surgery. The Biological Basis of Modern Surgical Practice. 15th ed.

D. C. Sabiston, Jr (ed.). 286 × 224mm. Pp. 2318. Illustrated. 1997 Philadelphia, Pennsylvania: W. B. Saunders. £84.

Sixty years ago, when modern surgery was in its childhood, the first edition of this book appeared. Since then surgery has evolved into its various subspecialties but the *Textbook of Surgery* has continued to address the generality of surgery and has grown, in its 15th edition, to an enormous 2318 pages in length and 5 kg in weight. definitely not a pocket book As with most surgical texts this is a volume rooted in pathology and it succeeds magnificently in its declared aim of explaining the biological basis of surgical practice. The author list reads like a 'Who's Who' of North American surgery and the authors bring a consistent magisterial quality to their writing. The book is very strong on basic surgical science and the management of surgical conditions, but clinical features are not emphasized This edition has six new chapters, including a useful overview of molecular biology in surgery and a fascinating exposition of the difficulties of measuring clinical outcome after surgery It is comprehensive and there must be very few problems or techniques in surgery that are not addressed (one might be surgery for arthritis). The illustrations are in black and white; many that were reproduced from other sources have suffered in the process The references are up to date but are sometimes excessive (for example, 141 for laparoscopic surgery). This volume is a member of the family of 'big American surgical textbooks' but one would have to say that it is a most impressive member. Every surgeon should have a book like this.

P. A. Grace

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Ireland

Endosurgery

J. Toouli, D. Gossot and J. G. Hunter (eds). 283 × 222mm. Pp. 1033. Illustrated. 1996. New York: Churchill Livingstone. £165.

This multiauthor textbook covers most aspects of laparoscopic, thoracoscopic and flexible endoscopic surgery. Although there are several similar books on the market, this is one of the most comprehensive of its kind; it is particularly up to date having made maximum use of modern communications technology to ensure rapid publication. It contains 105 chapters with a worldwide authorship of experienced clinicians, although only three of the 131 authors are from the UK. One particularly interesting feature is that the book is available on CD-ROM, with video sequences of the operative procedures (not reviewed), which is a formidable combination. Nineteen chapters are devoted to basic knowledge and technical aspects of the equipment, which are dealt with in great detail despite a paucity of information on suturing and knot-tying. The remaining chapters deal comprehensively with each organ system. There are some omissions of a minor nature: the section on bariatric surgery should have included some information about laparoscopic gastric banding; there was no mention of thoracoscopic splanchnicectomy for chronic pancreatic pain; there was no detail on the management of accessory bile ducts encountered during biliary surgery, and the operative details of total extraperitoneal hernia repair are difficult to follow. The sections throughout the book dealing with ultrasonographic diagnosis are outstanding. Overall, this is a reference work which deserves to find its way on to the shelf of all surgical units. It will be thoroughly consulted along with its CD-ROM. The editors are committed to regular updates which may well make this volume the best available of its kind.

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Ultrasound for the Surgeon

E. D. Staren and M. E. Arregui (eds). 285 × 220mm. Pp. 292. Illustrated. 1996. Philadelphia, Pennsylvania: Lippincott-Raven. £76.

Ultrasonographic examination of the body cavities might be expected to be as natural as extension of clinical examination to the surgeon as, for example, fibreoptic endoscopy is to the gastrointestinal clinician. With few exceptions, surgeons have not adopted ultrasonographic scanners for their personal use with any enthusiasm, preferring to use the skills of the trained radiologist or radiographer. This is strange, as immediate use of ultrasonographic imaging in the outpatient clinic or on the ward could dramatically shorten the diagnostic cycle.

This multiauthor book from Rush Medical College, Illinois, recognizes the potential to surgeons of advances in ultrasonography technology. The first chapter describes the principles of ultrasonography. There follow chapters on general and interventional abdominal, hepatobiliary, breast, vascular, endorectal, endoscopic and intraoperative ultrasonographic scanning. Curiously, many of the common uses of ultrasonography in general surgical practice, such as the assessment of lumps and bumps or of the thyroid, are barely mentioned. Many fields of surgery which may have a legitimate interest in ultrasonography diagnostics, for example, orthopaedic, thoracic and cardiac surgery, are overlooked entirely. I put this book down with some disappointment. It would have benefitted from more rigorous editing. The prose is somewhat longwinded and the composition of chapters is erratic. For example, the sections on diagnostic and interventional breast ultrasonography are five chapters apart. The pitch and tone is often more suited to a lay audience than to the postgraduate audience of busy surgeons for whom the book is presumably intended. The volume is liberally endowed with illustrations of ultrasonographic scans. These tend to disrupt the flow of the text and are often uninformative.

The authors are to be congratulated on their intent. Much valuable experience undoubtedly lies within the text, but the 'why to do it' rather drowns out the 'how to do it'. It is the latter education that most surgeons will seek, and it is to be hoped that a second edition will in due course redress the balance. Meanwhile, my reviewer's copy will grace the shelves of our medical school library for others to probe and to sound out.

D. Rew

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Bile Ducts and Bile Duct Stones

G. Berci and A. Cuschieri (eds). 284 × 220mm. Pp 179. Illustrated. 1997. Philadelphia, Pennsylvania: W. B. Saunders. £80.

This work summarizes the current state of the art in the management of laparoscopic cholelithotomy in the light of the personal experience of the contributors and the published literature. Considering that it is only 10 years since the first published description of laparoscopic cholecystectomy, the technical advances that have been made in the laparoscopic management of gallstones are very substantial. The authors are to be congratulated on producing such a comprehensive review which is both interesting, informative and challenging. The book fills a major gap in the market and, despite the rapid changes occurring in this field of surgery, it succeeds in remaining right up to date with technological advance, avoiding the common pitfall that besets many other technology based textbooks which are often out of date by the time of publication.

The contributors are all recognized experts within their field. Each chapter is well written with a forthright approach which encompasses all aspects of current controversy in a balanced and thoughtful manner. The main areas covered include the role of preoperative endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy, intraoperative fluorocholangiography and contact ultrasonography. The techniques of laparoscopic ductal stone clearance by various techniques are dealt with in depth. Further substantive chapters include conversion to open surgery, and the diagnosis and management of bile leakage. The text is complemented by a large number of high-quality illustrations The radiographs in the chapter concerning the anomalies of extrahepatic biliary ducts by Hamlin are particularly fascinating and provide a somewhat chastening experience. By contrast, the illustrations for the chapter on the repair of bile duct injury seem somewhat deficient and hopefully will be revised in future editions Great emphasis is laid on the role of intraoperative fluorocholangiography, as opposed to static imaging. Unfortunately, this is not routinely available in most UK centres, but the authors make an extremely good argument for its routine availability. Their view, that this should not be a selective part of laparoscopic stone surgery, is very difficult to argue against.

While many surgeons in the UK routinely undertake laparoscopic cholecystectomy, a large proportion of them may have little personal experience of the advanced techniques outlined in this text. Nevertheless, any general surgeon undertaking biliary surgery will find this an extremely stimulating read which will either fire his enthusiasm for advanced techniques or cause him to wonder whether he should be undertaking laparoscopic biliary surgery at all. This view is supported by the rather provocative statements of Professor David Fletcher in the chapter on the role of ERCP and endoscopic sphincterotomy in the laparoscopic management of gallstones where he states that 'those surgeons who feel incapable of managing all patients should leave the field of biliary surgery to those who are.....'. Overall, I found this a fascinating volume which succeeds in providing a state-of-the-art review which will be of interest to a wide readership. For those general surgeons undertaking laparoscopic biliary surgery who do not wish to embark on the learning curve associated with advanced techniques, it should be mandatory reading.

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Mastery of Surgery. 3rd ed. (2 volumes)

L. M. Nyhus, R. J. Baker and J. E. Fischer (eds). Both volumes: 285 × 220mm. Pp. 2400. Illustrated. 1996 Boston, Massachusetts· Little, Brown and Company. £220.

The editors claim an international authorship; only 29 of the 324 authors reside outwith North America My review is inevitably selective as a book which required hundreds of authors to write cannot be comprehensively analysed by a single individual, especially when it includes topics (for example, urology) that now lie well outside 'general surgery' The editors' target audience is 'non-urban' surgeons and trainees. Those readers will find the topic selection patchy and some important areas have either been omitted (benign breast disease is not even mentioned) or given scant attention (less than a page on primary varicose veins). Conversely, whole chapters have been devoted to specialist procedures (thoracoabdominal aneurysm) The editors have deliberately permitted some repetition but this has resulted in some substantial discrepancies (recommended prophylactic antibiotic regimens range from a single dose to 10 days) and an unbalanced text. Some options relevant to trainees are not discussed (only one approach to a femoral hernia is discussed) while there are four chapters devoted to rectal cancer resection. Sadly, three of the latter recommend rectal mobilization with a blunt hand thrust into the pelvis (ugh!) Some practices are unconventional (routine gastrostomy after colon surgery) Chapter formats range from text through to graphics more normally associated with an operative atlas As general surgeons become increasingly specialized, consultants will refer to specialist books and trainees need contemporary accounts of the basics. This book will satisfy neither and I cannot recommend it.

R. J. Aitken

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Notices and announcements

16 June 1997
Association of Coloproctology of Great Britain and Ireland Annual Meeting
Edinburgh, UK
Information: Association of Coloproctology of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

17–19 June 1997
European Council of Coloproctology Biennial Meeting
Edinburgh, UK
Information: Association of Coloproctology of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

25–28 June 1997
CAR '97. Computer Assisted Radiology and Surgery
Berlin, Germany
Information: CAR '97, c/o Technische Universitat Berlin, Institut fur Technische Informatik, Sekretariat CG, FR 3-3, Franklinstrasse 28/29, D-10587, Germany

7–8 July 1997
Rectal Cancer Workshop
Singapore
Information: Y H. Ho, Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 169608

13 July–22 August 1997
International Medical Students' Summer School
Manchester, UK
Information. Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

16–18 July 1997
British Association of Surgical Oncology 54th Scientific Meeting
Aberdeen, UK
Information: V. Hall, Administrator, BASO, The Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London WC2A 3PN, UK

26–27 July 1997
Hong Kong Surgical Forum – Summer 1997
Wanchai, Hong Kong
Information: Forum Secretary, Hong Kong Surgical Forum, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

31 August–3 September 1997
19th ESPEN Congress on Clinical Nutrition and Metabolism
Amsterdam, The Netherlands
Information: Van Namen and Westerlaken Congress Organisation Services, PO Box 1558, 6501 BN Nijmegen, The Netherlands

7–12 September 1997
8th International Congress on Cleft Palate and Related Craniofacial Anomalies
Singapore
Information: Dr L. Keuk, Organising Committee, Academy of Medicine, 16 College Road, Singapore 0316

12–17 October 1997
Management of Emergencies and Disasters: a Multidisciplinary Approach
Stoke, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

12–18 October 1997
Telemedicine and Telecare
Belfast, UK
Information. Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

15–22 October 1997
Cancer in Children: Challenges and Controversies
London, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

23–24 October 1997
2nd Nottingham International Colorectal Cancer Symposium
Nottingham, UK
Information: J. D Hardcastle, Department of Surgery, University Hospital, Nottingham NG7 2UH, UK

7–21 November 1997
Hong Kong International Cancer Congress and Asian Pacific Cancer Congress 1997
Hong Kong
Information: Gloria Wong, Cancer Centre, Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

9–14 November 1997
Health Technology Assessment: the Pathway to Evidence-Based Practice – the UK Experience
Manchester, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

25 February–1 March 1998
IX Asean Congress of Plastic Surgery
Penang, Malaysia
Information: M. Subramaniam, Department of Plastic Surgery, Hospital Ipoh, 30990 Ipoh, Perak, Malaysia

20–22 April 1998
The Paediatric Oesophagus. An Interdisciplinary Symposium. Main Topic: Gastro-Oesophageal Reflux with a Special Interest in Alkaline Reflux
Izmir, Turkey
Information: O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, 35100 Izmir, Turkey

13–15 May 1998
Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information: Association of Surgeons of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted. All manuscripts are submitted to editorial review.

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another journal, has not been accepted for publication elsewhere and has not already been published. **Any detected attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** In order to avoid subsequent embarrassment, authors are requested to submit with their manuscript copies of any other papers, either published, in press, or submitted for consideration elsewhere, which relate to the same subject. It is essential that publications or submissions using the same data set should be submitted to the Editors to allow assessment of any potential overlap with the submission to the Journal. The title page should indicate whether the paper is based on a previous communication to a society or other meeting. Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

Authors are requested to send three copies of original articles and other editorial matter to: The Editor, *The British Journal of Surgery*, Blackwell Science Ltd, 25 John Street, London WC1N 2BL, UK. Telephone: 0171 404 1831. Facsimile· 0171 404 1927. Books for review should be sent to the same address.

A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state whether an abstract of the work has been published and an appropriate reference should be given on the title page. Authors must disclose in the covering letter any potential or actual personal, political or financial interest they may have in the material, information or techniques described in the paper. The decision to publish or withhold such information will be made by the Editor. Sources of financial support for the work should also be acknowledged. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents. The Journal accepts the criteria for authorship proposed in the *British Medical Journal* (*BMJ* 1994; 308: 39–42). When a paper has many authors, they may be asked to justify the inclusion of all names listed. Results of multicentre studies should be reported under the name of the organizing study group. Methods of recognizing contributors have been proposed (*Lancet* 1995; 345: 668).

Following final approval of articles, authors are asked to submit the accepted version on disk. These should be IBM-compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, software, and disk system if known **Do not justify.** Particular attention should be taken to ensure that any articles submitted adhere **exactly** to Journal style in all respects. Please send us digital versions of your figures. Ideally, these should be sent in native format or PICT if created on a Mac, or in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Avoid using tints if possible; if they are essential to the understanding of the figure, try to make them coarse. Further details can be obtained from the publisher. Disks will not be returned to authors.

Rejected manuscripts and illustrations will not be returned to the authors, unless this is specifically requested.

Ethics

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethics committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs that might identify an individual. Evidence of such consent should be submitted with the manuscript.

Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts, which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988, 296: 401–5 or the *Annals of Internal Medicine* 1988; 108: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the brief name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal believes that this information is essential for any reader who wishes to obtain similar material Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a abstract of no more than 200 words on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation. **Randomized controlled trials** should be clearly identified as such in the title and abstract.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no abstract is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 400 words (300 if accompanied by a figure), with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications that may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4-cm margins. Manuscripts that do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, abstract, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction, methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support, and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Abstract

The second page of the manuscript should carry an abstract of not more than 200 words This should be broken into four paragraphs each with a clear heading as follows. *Background·* this should state why the study was done, and its main aim; *Method·* this should describe patients, laboratory material and other methods used, *Results.* the main findings of the study should be stated briefly, including important numerical values; *Conclusion:* the main conclusion drawn from the Results should be stated. Controversial or unexpected observations may be highlighted, but this section should be brief. The summary should identify clearly the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. It should be written in clear prose

Tables and illustrations

Three copies of all illustrations and tables should be submitted Each table with an appropriate brief title should be typed on a separate page. Line drawings are acceptable as clear black on white graphics, computer printout or photocopies. Radiographs, photomicrographs, etc should be submitted in the form of glossy prints, original transparencies or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. If a table or an illustration has been reproduced from a published work the original source must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension by the reader. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator

In the text, references should be numbered consecutively by superscript: ^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper, journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number; page numbers For example. De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; 66: 184–6 The sequence for the chapters of a book should be. author(s), chapter title, editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York. Springer, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *Br J Surg* 1991; 78: 782–4 The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of data, the *analysis* of data and the *interpretation* of results.

Design

Authors should set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the *P* value. For example, '$t = 1{\cdot}34$, 16 d f., $P = 0{\cdot}20$' might be reported Actual *P* values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

British Journal of Surgery 1997, 84, 737–738

Leading articles

Surgical research and randomized trials

Recent articles have criticized clinical surgical research, suggesting that many of the trials published have not been carried out in a scientific fashion and are therefore largely meaningless[1]. There is little doubt that the best foundation on which to make clinical decisions is a properly randomized clinical trial as described by Sackett[2]. Level one, the best evidence, is a randomized trial with a low rate of false-positive or false-negative errors. Level two evidence is a randomized trial with high levels of false-positive or false-negative errors. Level three evidence is a non-randomized concurrent cohort comparison, level four a non-randomized historical cohort comparison and level five a series of cases without controls. Is it true, then, that much surgical research is poor[3], tending to assess the quality of surgical procedures inadequately, or is the case being overstated?

The surgical community responded to the article in the *Lancet* by Horton[1] by pointing out the problems that face surgical researchers. These include a lack of funding for clinical research, recognized by the establishment of the National Health Service Executive and the provision of research fellowships by the Royal Colleges of Surgeons[4]. Apart from this consideration there is a basic lack of understanding by physicians and epidemiologists of the need to do an operation properly and consistently. If this is not done, variability is produced in any trial as a result of the learning curve of surgeons undertaking a new procedure. This type of error is not a problem when comparing medications and it adds another dimension to randomized surgical trials. For these reasons the correct method of assessing the effect of a new surgical procedure is an initial article describing the new technique and outlining the results of the operation. This should be followed by other surgeons, having learned the method, describing their own experience with it; feasibility studies should be carried out and audited by others. These descriptive clinical papers should not be disparaged by the scientific community; they are essential before embarking on randomized trials. To obtain sufficient power, randomized studies must be multicentred, and an audit of procedures on a national basis is the correct way to proceed. Having said this, we must not remain smug or ignore the criticisms of others. We should try to convince them by rational argument of the merits of our work, but we must also respond to reasonable criticism.

Although many surgical publications state that a randomized trial has been performed, there is little doubt that the information provided is often minimal, making it hard for the reader to be certain that the trial has been carried out properly. Two recent publications discussing clinical trials[5,6] set out the standards for reporting such research. These papers did not particularly single out surgical research but listed the items that should be included generally in reports of randomized studies. The so-called CONSORT (Consolidated Standards of Reporting Trials) statement describes the ideal situation that one would aim to achieve in any randomized clinical trial, and an article by Liem and colleagues[7] in this issue of the Journal (see pages 769–70) argues that we should all adhere to these new criteria and that editors should accept only papers that do so.

It is hard to argue with this suggestion and in an ideal world every item of the 21 listed in the CONSORT statement would be documented when describing a trial. However, space is often limited in journals and it is surely unnecessary to mention every single item listed in the CONSORT paper. Perhaps editors should provide referees with the full checklist to enable them to decide whether an article fulfils the requirements for a proper study. It may even be sensible to modify the recommendations, highlighting certain mandatory items such as ensuring that all patients who were not randomized and those who were otherwise excluded are recorded, along with the reasons for non-randomization and exclusion. Endpoints should be defined clearly and intention to treat recognized as an important element of the whole process. This is the basic minimum that we should require while attempting to introduce all of the CONSORT items.

Surgeons, by their nature, are enthusiasts and we must not pour cold water on their efforts to improve methods of treating patients. However, we must learn to prove that what we believe to be best is indeed better than existing techniques, or we will receive little support from the rest of the medical community, who reasonably believe that operations are to be avoided at all costs. In the new era of evidence-based medicine, this is becoming increasingly important. We should have learned a lesson from the introduction of laparoscopic surgery which, without any evidence, was embraced by the surgical community as a 'new toy'. It is only now that trials, such as the one reported by Majeed *et al.*[8], are appearing and demonstrating (sometimes to our dismay) that new toys are not always the best ones.

Endovascular surgery[9] is another area for which there are no comparative data to compare new methods with existing ones. In spite of this, new techniques continue to be described on the basis that technology advances so rapidly that meaningful trials cannot be carried out. Surgeons are not disinclined to instigate proper trials but they do need help in order to carry them out properly, and the current method of peer review[10] of grant applications is perhaps not the best way of allowing or encouraging trials to continue. Multicentre randomized studies, after appropriate audit and feasibility studies, are hard to produce and require assistance from epidemiologists in particular. Grant-giving authorities and others should recognize the importance of surgical research and the need to help surgeons who wish to become involved to do it properly, by assisting them financially. Let us welcome the CONSORT statement and try to adhere to it, accepting the more sensible suggestions but not being carried away by a cascade of nitpicking and unnecessary requirements. Randomized trials, although important, are not the be all and end all of every paper in surgical practice. Those describing technique and using current cohort controls in feasibility studies are perfectly adequate and have been responsible for considerable progress in surgery.

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Laryngeal transplantation

After a 20-year pause, research into laryngeal transplantation is now resuming. It is therefore timely to consider whether this attention is justified.

Is laryngeal transplantation desirable?

The effects of irreversible disease of the larynx are devastating. Loss of airway due to tumour or stenosis is life threatening, as is loss of sphincter function, while loss of phonation severely impairs quality of life. Laryngectomy can deal with aspiration and obstruction at laryngeal level, but it results in permanent functional, communicative, cosmetic and psychological disability. The recent introduction of speaking valves has improved the rehabilitation of patients after laryngectomy, but vocalization remains far from normal, and patients retain a stoma with its associated cosmetic and psychosocial disability. Non-viable airway replacements have been helpful for the trachea[1], but they are insufficient to secure laryngeal function, where viability is essential.

A UK survey of 372 patients after laryngectomy has shown that three-quarters would like to receive a laryngeal transplant if it were safe to do so. This figure remained at 50 per cent even if there was little chance of normal speech, but only 20 per cent would accept a graft if long-term systemic immunosuppression were required[2].

Is laryngeal transplantation practical?

There are reasons to believe that the problems faced by early researchers might now be overcome. Microvascular transfer is now routine in head and neck surgery. Viability of canine tracheal transplants depends on the thyroid vessels[3], which also supply the larynx in humans, and so should support a laryngeal graft.

Advances in immunosuppression include the introduction of less toxic agents, such as mycophenolate mofetil[4], and research into various means of inducing specific tolerance is producing encouraging results. While immunosuppression might be associated with an enhanced risk of tumour recurrence, as suggested by studies of Scandinavian transplant recipients[5], the results of liver transplantation for neoplasia suggest that early recurrence may not be such a major problem[6].

Interruption of recurrent laryngeal nerves may lead to hoarseness, stridor, ineffective cough, or aspiration of food and saliva. Historically, attempts at restoration of cord movement after congenital or acquired paresis have met with mixed success in humans and animals[7].

What research is required?

It is unclear from published studies whether transplanting the larynx results in a viable organ with intact mucosa, cartilage and muscle, or whether the graft merely provides a scaffold, similar to that provided by the preserved trachea. If viability is confirmed, the balance between damage due to ischaemia and that due to immunological injury, and the time course of these events, need clarification. Such studies would provide useful insight into the graft–host interaction in transplanted airway mucosa. What happens to cartilage when transplanted is an interesting side issue that has not been studied to date.

In pigs, the development of operational tolerance, in which immunosuppression is no longer required after a period of time, may depend on the degree of swine leucocyte antigen (SLA) matching between host and donor, and on the organ concerned. It is important to determine the position of the larynx in the spectrum of operational tolerance of organs, as this will ultimately determine the degree of matching and immunomodulation necessary, and therefore the availability of possible donor organs.

The greatest problem facing those researching into laryngeal transplantation is that of reinnervation. Unlike clinical transplant settings so far, laryngeal transplantation involves immediate nerve repair; this is relatively unexplored. Various combinations of reinnervation, with or without growth factors, require study. Although, to date, there has been no imperative for restoration of the sensation associated with superior laryngeal nerve function, this strategy might theoretically prevent aspiration while recurrent nerve function is being regained.

Is there a suitable model?

Early studies into laryngeal transplantation used dogs[8]. Mortality was high, partly because of the sensitivity of dogs to immunosuppressants. More recent studies have used rats[9], allowing bigger experiments than are usually possible with large animals. However, the model used has been that of a heterotopic, sealed-off allograft, which introduces the confounding factor of microbiological variability. Laryngeal anatomy in both animals is distinct from that in humans.

The pig larynx is structurally similar to the human organ. Piglets have been used successfully to study surgical interventions in the larynx, and adult Large Whites are currently being employed to investigate transplantation of the trachea[10]. Various phenotypes of Minipig are available, making studies of transplantation across various SLA barriers possible. The possibility of the pig as a source of xenotransplants may also be of relevance in the long term. The pig, therefore, appears to be the best candidate for an experimental model.

Conclusion

As advances in immunosuppression and immunomodulation progress, it becomes pertinent to consider transplanting organs whose loss is not, in itself, life threatening, but which causes enormous impairment to quality of life. Loss of a functioning larynx leads to severe physical and psychological morbidity. The successful clinical application of laryngeal transplantation offers an attractive solution to the problems associated with laryngectomy, but some important questions remain to be answered. The pig appears to provide a suitable model in which to explore these questions. Considerable research is required before clinical translation can be contemplated, but to those faced with life without a larynx this effort will surely seem well worthwhile.

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Review

Aggressive multimodality treatment for locally advanced irresectable rectal cancer

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Background Local failure rates are high for locally irresectable primary or recurrent colorectal cancer, even when chemoradiation therapy is employed.

Aim This review evaluates evidence supporting aggressive preoperative chemoradiation followed by maximal surgical resection and intraoperative radiation therapy to achieve disease control and cure for patients with locally advanced irresectable primary or recurrent rectal cancer.

Results A 5-year survival rate of 42 per cent with a central failure rate of 2 per cent may be achieved in patients with locally irresectable primary rectal cancer. In patients with locally recurrent disease, these values at 5 years are 18 and 28 per cent respectively. The 5-year incidence of distant metastasis remains high, affecting 64 per cent of patients with primary cancer and 75 per cent of those with recurrent cancer.

Conclusion A disease-free surgical resection margin remains paramount to achieve cure. Encouraging trends exist, however, for further evaluation of multimodality therapy as a means of reducing local recurrence of disease.

Locally advanced irresectable colorectal cancer, when left untreated, results in a median survival of only 7·8 months[1]. While *en bloc* resection of adjacent organs is often possible for local tumour extension, local and systemic failure rates remain high with 5-year survival rates of only 19–33 per cent with surgery alone[2–6]. Furthermore, lateral extension of tumour to pelvic side walls precludes curative *en bloc* resection, and palliative resection improves survival only marginally to a mean of 10·9 months[1]. Thus patients with irresectable rectal cancer not only have a short life expectancy but also often have disabling symptoms, including unrelenting pain. The use of chemoradiation for tumour downstaging may increase the chance of resectability and reduce the incidence of local and systemic failure, thereby making this combined modality therapy an important option. This review addresses such therapy, including the role of intraoperative radiation therapy in the treatment of primary (stage $T_4 N_{1-3} M_0$) or localized recurrent 'irresectable' colorectal cancer.

External beam radiotherapy for advanced rectal cancer: current role and limitations

The rationale for irradiation as a component of adjuvant treatment in rectal cancer is based on the risks of local recurrence after surgery alone, especially when complete excision has not been achieved[7]. Evidence of the radioresponsiveness of rectal cancers must also be considered[8,9].

External beam radiation therapy (EBRT) alone can provide short-term palliation for locally advanced irresectable rectal cancer in 70 per cent of patients[10–12]. However, 5-year survival is achieved in only 2–5 per cent of these patients[10–12]. Doses that can be delivered safely are often less than 60 Gy, whereas doses that are required to achieve 'curative' intent are in excess of 60 Gy. Small bowel and large bowel toxicity remain the primary restrictions to the delivery of high doses[9,13].

External beam irradiation combined with surgery diminishes the rate of local recurrence both in prospective non-randomized and in randomized preoperative and postoperative trials where complete resection has been achieved[14–17]; possibly it improves overall survival[15,18]. For irresectable tumours, salvage surgery following EBRT doses of 40–50 Gy in 1·8–2·0-Gy fractions over 4–8 weeks has been associated with a 5-year survival rate of 23 per cent for patients with fixed lesions, compared with 0 per cent when surgery has not been carried out[12]. The logical approach for locally advanced irresectable colorectal cancer is, therefore, to combine surgery with irradiation.

Preoperative *versus* postoperative external beam radiation therapy for locally advanced irresectable colorectal cancer

The primary advantage of postoperative EBRT is that firm evidence of the need for additional therapy based on the presence of positive resection margins and the absence of metastatic disease is confidently established. Long-term local and systemic failure rates are high with this approach, however. Schild and colleagues[19] reported on 17 patients who were treated with submaximal resection followed by 40–60 Gy of fractionated EBRT in 1·8–2·0-Gy fractions, 5 days per week. Ten patients had microscopic and seven had macroscopic residual disease. Thirteen of the 17 patients suffered a local recurrence, and ten of them had systemic disease within 3 years. The overall disease-free survival rate for these patients was 24 per cent at 5 years; median survival was 18 months.

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Allee and associates[20] reported a similar series of 56 patients in which the local failure rates in those with microscopic residual (surgically suspected or pathologically proven) or macroscopic residual disease were 30 and 57 per cent respectively. The 5-year survival rate for these same groups was 45 and 11 per cent respectively. Small bowel toxicity was a problem in this study with 9 per cent of patients requiring surgery for this complication. Nevertheless, it was noted that radiation-related benefits in the setting of microscopic residual disease were dose dependent: doses greater than 60 Gy were associated with a local failure rate of only 11 per cent, compared with 33 per cent for doses of less than 55 Gy. In all, postoperative irradiation for incompletely resected tumours assures that patients are appropriately selected, but offers only limited freedom from recurrence.

With the aim of increasing the prospect of curative surgery, preoperative EBRT for locally advanced irresectable rectal cancer has been considered[15-31]. In support of the concept that preoperative radiation therapy may downstage the disease, several studies demonstrate that clinically irresectable lesions can be converted to resectable tumours with reduced tumour proliferation, with rates of 'resectability' ranging from 40 per cent to as high as 88 per cent, local failure rates of between 7 and 50 per cent, and 5-year survival rates of 12–34 per cent[21-34]. Even though preoperative EBRT converts most patients from being 'irresectable' (stage T_4) to 'resectable', results still do not approach those considered acceptable for patients undergoing 'curative' surgery for resectable tumours (stage T_{1-3})[35-40].

Although the majority of lesions become resectable following radiation therapy, not all will be amenable to complete resection. For example, in a series of 44 clinically irresectable lesions, 33 were considered resectable after preoperative irradiation and, therefore, taken to surgery[22]. Of these 33 cases, 26 were reported as complete resections. The significance of a complete resection is clearly established in this report by the fact that 18 of the 26 completely resected patients were alive after a minimum follow-up of 36 months, whereas mean survival in the incompletely resected group was only 17 months.

The risk of overtreating patients with early disease remains a possibility, but there are several advantages of preoperative EBRT in those with locally advanced primary or recurrent rectal cancer. Perioperative morbidity associated with initial resection is not insignificant and, if postoperative complications ensue, the delay to postoperative EBRT and chemotherapy can result in loss of therapeutic benefit. Possible tumour shrinkage with an increased possibility of achieving gross total resection has also been reported with the preoperative approach[21-34]. Finally, preoperative EBRT has been associated with a lower incidence of local and, in some series, systemic failure where complete resection has been achieved, suggesting a potential influence on tumour dissemination with this approach[15,18,22-32].

Preoperative radiation therapy results in increased rates of resection where negative margins are achieved and lower local failure rates are accomplished. Local failure, however, is still commonplace in patients receiving preoperative EBRT and it does not address the problem of systemic failure. Overall survival rates remain low at 14–28 per cent in the presence of residual disease, and 29–43 per cent when surgical resection is complete[22-32]. Additional therapies to enhance the effective dose of EBRT and to address the issue of systemic failure, which occurs in 50–80 per cent of patients, should be considered. Chemotherapy seems a logical additional treatment. Modest evidence of improved local and systemic failure reduction from preoperative and postoperative chemoradiation trials for resectable cancer have encouraged a similar approach for locally advanced rectal cancer.

Combined chemoradiation therapy for locally advanced rectal cancer

In separate analyses at the Mayo Clinic, EBRT has been used alone or in combination with chemotherapy, immunotherapy, surgical resection or intraoperative radiation therapy (IORT) for the treatment of locally advanced irresectable colorectal cancer. Early series combined results from primary and locally recurrent colorectal cancers. The first series contained 65 patients with locally irresectable primary or recurrent colorectal cancer who were assigned randomly to receive either 40 Gy EBRT and 5-fluorouracil (5-FU) (15 mg/kg on the first 3 days of EBRT) or 40 Gy EBRT and placebo over 4 weeks[41]. Median survival was 10·5 months in the placebo plus EBRT group *versus* 16 months in those having EBRT and 5-FU ($P < 0·05$).

In a second study from the Mayo Clinic, 44 patients with locally advanced rectal cancer (seven irresectable, seven resected but residual, 30 locally recurrent) received 50-Gy split-course postoperative pelvic EBRT with or without adjuvant immunotherapy[42]. Local progression within the EBRT field was diagnosed in 28 patients. In 17 of the 31 evaluable patients, it was the only site of relapse. Median survival was similar at 18 months for both patient groups.

Partial or complete response rates have been reported in several more recent series of patients with locally advanced rectal cancer when 5-FU plus leucovorin regimens have been used. Moertel and colleagues[43] reported outcome in ten patients with locally recurrent irresectable or residual sigmoid or rectal cancer who received 5-FU, leucovorin and EBRT (45–50 Gy), with or without IORT. Median survival was 31 months, and two patients had a disease-free survival period of 38 and 50 months. In a series of 429 patients with metastatic colorectal cancer, 5-FU plus low- or high-dose leucovorin improved median survival compared with 5-FU alone[44].

Memorial Sloan-Kettering investigators compared the effects of preoperative EBRT in primary resectable and irresectable disease, in the presence and absence of systemic chemotherapy. Accordingly, 20 patients with irresectable disease received preoperative EBRT plus 5-FU and leucovorin, 11 with irresectable disease received preoperative EBRT alone, and 21 with primary resectable disease received preoperative EBRT alone[30]. Patients who were deemed to have irresectable disease before operation but received 5-FU–leucovorin and EBRT had a higher complete response rate (20 *versus* 6 per cent) and a lower incidence of positive nodes (30 *versus* 53 per cent) than those who had primary resectable disease and received preoperative EBRT alone. Furthermore, of patients with initially irresectable disease, the subsequent resectability rate was higher in those who received preoperative chemoradiation and EBRT than in those who received radiation therapy alone (90 *versus* 64 per cent respectively). Similar improvements in the rates of resectability and curative resection have been reported by others[45,46].

Preoperative combined chemoradiation therapy has the theoretical benefit of starting the systemic component of the treatment at an earlier interval, before resection, with a potential impact on established or circulating tumour cells. A radiosensitizing effect has been reported with 5-FU, which may also have an effect on downstaging of local disease[30,31,41–46]. A further advantage is that toxicity rates may be lower when chemoradiation is delivered before rather than after operation, although this has not been shown in randomized controlled trials[30].

Use of combined chemoradiation therapy followed by surgery for locally advanced irresectable tumour has resulted in reported disease-free survival rates of 60–83 per cent, with a follow-up period of 20–36 months[31,44–46].

Despite the improvements achieved by preoperative combined chemotherapy and EBRT in terms of tumour downstaging and increasing rates of surgical resection with negative margins, local failure rates of up to 29 per cent are still reported[11,45–47]. Concern remains about local and systemic failure rates in patients who receive radiosensitizing doses of chemotherapy and radiation followed by surgical resection, in whom there remains microscopic or macroscopic residual disease. Local control and long-term survival for these patients remains a problem. When gross total resection cannot be accomplished, it is difficult to achieve local control, even with the addition of EBRT and limited cycles of chemotherapy. The addition of further cycles of chemotherapy in the postoperative period may address the issue of systemic failure. Small bowel toxicity prevents delivery of higher doses of EBRT to increase local control[9,13,48,49]. One option for improved local control is to deliver IORT as a boost to the effects of the external component[47,50–61].

Rationale for intraoperative radiation therapy

IORT in its broadest sense refers to the delivery of radiation at the time of surgery. This allows for the delivery of high biologically equivalent and locally effective doses of radiation while dose-limiting structures are displaced. EBRT where there is residual disease after surgical resection is usually only palliative, because doses greater than 60 Gy in 25–28 fractions cannot be delivered safely[9,13]. When it is envisaged that surgical excision alone will be insufficient, a preferred treatment alternative is to give tolerable external doses of 45–50 Gy before operation in 1·8–2·0-Gy fractions and to deliver the remaining radiation at surgery when dose-limiting organs may be protected.

The biological effectiveness of single-dose IORT is considered equivalent to two to three times the equivalent dose of fractionated EBRT[50]. Therefore, the effective dose in the IORT boost field, when added to the 45–50 Gy given with EBRT, is 65–80 Gy for an IORT dose of 10 Gy, 75–95 Gy with a 15-Gy boost, and 85–110 Gy with a 20-Gy IORT dose.

IORT with electrons (IOERT) and with high-dose brachytherapy (IOHDR) are currently available methods of delivering such treatment. While a dedicated theatre suite with suitable lead shielding is ideal for both approaches, IOHDR enjoys the advantage of using a mobile afterloading machine. The primary differences between IOERT and IOHDR are summarized in *Table 1*.

Table 1 Summary of the differences between intraoperative radiation therapy with electrons and intraoperative high-dose brachytherapy

	IOERT	IOHDR
Treatment time (min)	20–45	30–120
Surface dose (< 1 cm tumour thickness)	90 per cent of maximum dose	Greater than IOERT
Dose at > 1 cm depth	> 90 per cent of maximum dose	Not adequate
Pelvic access	Rigid cone fields and limited by anatomy	Wherever FLAB can be packed in position

IOERT, intraoperative radiation therapy with electrons; IOHDR, intraoperative high-dose brachytherapy; FLAB, flexible afterloaded brachytherapy

The need for technical support and high equipment costs remain primary disadvantages of both methods.

The combination of IOERT or IOHDR with external beam irradiation and chemotherapy has the potential of improving the therapeutic ratio of local control *versus* toxicity in the following ways: (a) a decrease in the volume of the irradiation boost field by direct tumour visualization and appositional treatment; (b) exclusion of all or a part of the dose-limiting structures by operative mobilization, shielding or use of appropriate energies: and (c) an increase in the effective dosage delivered by a combination of (a) and (b).

Intraoperative radiation therapy with electrons for primary locally advanced rectal cancer

A linear accelerator is used to generate an electron beam of variable energy, 6–18 MeV, depending on the maximum depth of disease. Lower energies are used after gross total resection or with minimal residual disease. IOERT dose is calculated at the 90 per cent isodose line and is dependent on the amount of disease remaining after maximal resection. Common guidelines used at the Mayo Clinic for dose *versus* amount of residual disease are as follows: 7·5–12·5 Gy for negative but narrow margins; 10–12·5 Gy for microscopic residual disease; 15 Gy for gross residual disease present with largest dimension of less than 2 cm; and 17·5–20 Gy for unresected or gross residual disease with largest diameter greater than 2 cm. If the lesion has recurred within a previous surgical bed, the minimum IOERT dose is often 15 Gy in view of concerns about a hypoxic tumour bed[47,50,51].

Controlled IOERT trial results are not available as yet. However, differences between historical (non-IOERT) and current (IOERT) results provide strong evidence of the efficacy of this therapy (*Table 2*). In an initial report on 32 patients from the Massachusetts General Hospital, IOERT appeared to improve local control in patients with either residual disease after maximal resection or lesions that were initially irresectable for cure[53]. Local control and survival were better in the latter group of 16 patients, compared with a similar historical group of 17 patients treated by preoperative EBRT and surgery alone. The local relapse rates were 43 per cent for EBRT and surgery compared with 0 per cent for EBRT, surgery and IOERT.

Table 2 Comparison of external beam radiation therapy and surgery *versus* external beam radiation therapy, surgery and intraoperative radiation therapy with electrons for locally advanced primary rectal cancer: the Mayo Clinic experience (1981–1994)

	EBRT	EBRT and IOERT
No. of patients	17	55
Survival rate (%)		
3 years	24	53
5 years	24	42
Local failure rate (%)		
3 years	76	18
5 years	76	18
Distant failure rate (%)		
3 years	59	49
5 years	59	64
Central failure rate (%)		
3 years	—	2
5 years	—	2

EBRT, external beam radiation therapy; IOERT, intraoperative radiation therapy with electrons

In a more recent report from the same institution, the 5-year actuarial survival rate was 43 per cent in 42 patients who received IOERT plus EBRT for locally advanced primary rectal cancer[54]. Both 5-year actuarial local control and disease-free survival rates were improved if the surgeon was able to perform gross total resection before IOERT. Data from the Rush Presbyterian Group have supported the correlation between local tumour control and the amount of residual disease after resection of primary disease in patients who received IOERT as a treatment component[55].

Similar survival rates and disease control can be derived from the Mayo Clinic experience of two sequential series of 17 patients having no IOERT[19] and 55 receiving IOERT[56] who were treated for locally advanced non-metastatic primary rectal cancer (*Table 2*). There was local disease relapse in 76 per cent of patients who did not receive IOERT within 18 months of surgery, whereas the local relapse rate was 18 per cent in those who had IOERT. The improvement in local control appeared to translate into improved 3- and 5-year survival rates associated with IOERT and no IOERT of 53 *versus* 24 per cent and 42 *versus* 24 per cent respectively ($P<0{\cdot}0006$). Although this was not a randomized trial, it suggests that the addition of IOERT substantially reduces the local failure rate.

Intraoperative high-dose brachytherapy for primary advanced rectal cancer

It can be difficult with IOERT to encompass the tumour bed or residual tumour in patients with deep pelvic disease, especially with anterior disease or a narrow deep pelvis. As a result, a flexible device made of vinyl plastic on a synthetic oil base with 12 channels that traverse its middle has been designed. This allows direct apposition of radiation from a 12-channel high dose rate afterloading machine with an iridium-192 source[57]. This method is also known as the FLAB (flexible afterloaded brachytherapy) method. Because of its flexibility, FLAB can conform to the shape of the surface to which it is applied. In particular, it is ideal for curved or complex surfaces, such as pelvic sidewalls, the presacral area, the pubic region and other abdominal wall surfaces. The material is translucent, allowing placement of the device on to the desired surface under direct vision. The radiation dose delivered by IOHDR is limited by its penetration of up to 1 cm. Anterior tumours with a maximum thickness of 5 mm of residual disease appear most suitable for this method[57].

In Munich, where this technique has been developed, 56 patients who were staged before operation as having T_3 or T_4 primary rectal cancer have undergone resection and IOHDR, combined with preoperative or postoperative chemoradiotherapy[58]. Eighteen patients did not complete the protocol, either because they had been overstaged and did not require postoperative adjuvant treatment (15 patients), did not receive adjuvant treatment because of postoperative morbidity or because they were understaged before operation and were found to have diffuse distal metastases at surgery (two). There were five local recurrences, three in 19 patients with T_3 lesions and two in 19 with T_4 tumours after 25·5 months of follow-up. Only one local recurrence was identified within the EBRT field, with no recorded recurrences within the IOHDR field.

A clear downstaging effect was observed in 17 patients with clinical stage $T_4N_1M_0$ disease who had received preoperative chemoradiotherapy. Following adjuvant treatment, histopathological staging demonstrated that 14 patients were downstaged: to T_2N_0 in one patient, T_3N_0 in 11 and to T_4N_0 in two. Two other patients were restaged as T_3N_2. In contrast, of the 19 patients who had T_3 tumours and received postoperative adjuvant chemoradiotherapy, ten were found to have metastatic tumour within regional lymph nodes.

The Memorial Sloane-Kettering experience with IOHDR in 30 patients with primary irresectable rectal cancer corroborates these findings, although the data are preliminary[59]. To date, ten patients with primary locally advanced cancer have been treated in this way with a mean follow-up of 8 months. Actuarial local control at 1 year was achieved in 86 per cent of patients, with a disease-free survival rate of 57 per cent. Similar results have recently been reported from Rome[60] and Los Angeles[61].

The combination of preoperative chemoradiation therapy followed by maximal surgical resection and IORT, therefore, appears to improve local control and offer the best chance of cure for patients who have locally advanced and otherwise irresectable rectal cancer. These observations remain to be confirmed by a randomized controlled trial.

External beam and intraoperative radiation therapy in patients undergoing curative surgery for recurrent rectal cancer

Between 7 and 33 per cent of patients with rectal cancer treated for cure will develop isolated locoregional recurrence[62–72]. Autopsy series suggest that 25–50 per cent of patients with locoregional recurrence have cancer confined to the pelvis at the time of death[71,72]. In the absence of surgical intervention, less than 5 per cent of these patients survive up to 5 years[62,64,70]. Locally aggressive therapies that could palliate and/or potentially cure these patients would seem justified.

The Massachusetts General Hospital experience with IOERT as a supplement to EBRT and surgery showed, in a series of 30 patients who underwent surgery for locally recurrent tumour, that 5-year local control of disease was achieved in 42 per cent when complete resection was possible; this was associated with a 5-year survival rate of 33 per cent. Resection was incomplete in 17 patients and local control was achieved in only 11 per cent at 5 years, with a 6 per cent survival rate. The 5-year actuarial survival rate for all patients was 19 per cent[53]. In an updated analysis of 41 patients, those with gross residual disease had 5-year local control and disease-free survival rates of 21 and 7 per cent respectively. This compared with rates of 49 per cent for local control and of 21 per cent for disease-free survival at 5 years in patients in whom gross total resection was achieved with clear or microscopically positive margins[54]. Similar data from other workers[55,73,74] support the concept of achieving local tumour control by maximal reduction of the residual disease during surgical resection

The early Mayo Clinic experience of 59 patients who presented for surgery for local pelvic recurrence of disease combined with EBRT and IOERT was a 4-year survival rate of 34 per cent, a local failure rate of 40 per cent and distant failure rate of 39 per cent[50]. A more recent review with 116 patients undergoing curative surgery for locally recurrent rectal cancer found that the 3- and 5-year actuarial survival rates of these patients were 34 and 18 per cent respectively. The cumulative probability of local failure was 27 and 40 per cent, and of distant metastasis 67 and 75 per cent, at 3 and 5 years respectively (*Table 3*). Similar results have been reported from other centres that have an IOERT capability[47,53,54,73,74].

Table 3 Disease control and survival with and without regimens containing intraoperative radiation therapy with electrons for locally recurrent colorectal cancer: the Mayo Clinic experience (1981–1994)

	No IOERT	With IOERT
No. of patients	64	116
Survival rate (%)		
3 years	18	34
5 years	7	18
Local failure rate (%)		
3 years	93	27
5 years	—	40
Distant failure rate (%)		
3 years	54	67
5 years	—	75
Central failure rate (%)		
3 years	—	13
5 years	—	28

IOERT, intraoperative radiation therapy with electrons

Does intraoperative radiation therapy have a role in patients with recurrent rectal cancer undergoing palliative surgery?

In a Mayo Clinic analysis of 106 patients without extrapelvic disease treated by palliative resection between 1981 and 1988, 42 received IOERT as a component of treatment[75]. In 34 of the 42, gross residual disease remained after attempts at resection, with microscopic residual disease present in the remainder. External irradiation was also delivered to 41 patients, with 45 Gy given to 38. The survival rate was influenced most significantly by the amount of residual disease (5-year survival: microscopic 33 per cent *versus* macroscopic 9 per cent), by the delivery of IOERT (5-year survival: IOERT 19 per cent *versus* no IOERT 7 per cent, $P<0{\cdot}0006$), by the presence of pain as a symptom (3-year survival: asymptomatic 49 per cent *versus* symptomatic without pain 7 per cent or symptomatic with pain 28 per cent) and by the degree of tumour fixation (no fixation or fixation at one site 45 per cent at 3 years *versus* fixation at two sites 29 per cent *versus* fixation at three sites 0 per cent). For patients having IOERT, the 3-year survival rate with gross residual disease or the presence of pain as a symptom was 44 and 43 per cent respectively, compared with less than 20 per cent in those who did not receive IOERT.

A more recent analysis[77] of 80 patients with recurrent rectal cancer receiving preoperative chemoradiation followed by surgery and IOERT has shown the 5-year survival rate in patients with locally recurrent cancer to be 20 per cent.

In an analysis by Suzuki *et al.*[75], 37 of 106 patients received EBRT as the only method of irradiation. The 2-year survival rate was only 16·7 per cent, compared with 62 per cent in a group receiving IOERT[77]. A more recent analysis at the Mayo Clinic of 80 patients has confirmed this 2-year survival pattern after IOERT, with a rate of 64 per cent[77] Furthermore, the 5-year survival rate was 7 per cent in patients having EBRT and surgery alone, compared with 20 per cent when IOERT was given[77]. In previous EBRT analyses of patients with locally recurrent tumour, local regression was documented in 90 per cent of patients, compared with 40 per cent when IOERT was delivered[42,76,77].

Radiation therapy as a component of aggressive multimodality treatment in patients with recurrent cancer who have received previous external beam radiation therapy

Fifty-two patients who presented with local or regional relapse after previous adjuvant EBRT and chemotherapy were treated with further surgery and IOERT[79]. Additional EBRT was given to 37 of these patients. The median dose delivered was 25·2 (range 5–50·4) Gy. The EBRT target volume was usually recurrent tumour as defined on computed tomography plus a 2-cm margin. Surgery and IOERT were performed within 0–2 weeks of EBRT. Median survival was 23 months for the group, with 2- and 5-year survival rates of 48 and 13 per cent respectively. These results are similar to those observed in patients with locally advanced primary disease who received EBRT but no IOERT[19]. The local relapse rate was higher in IOERT-treated patients who had received previous EBRT before development of the recurrence (56 per cent), compared with that in those who had not received EBRT (26 per cent). Rates of central relapse were lower for the former group when the dose of EBRT was greater than 30 Gy, with a 2-year rate of local control of 81 per cent, compared with rates in those who had received less than 30 Gy EBRT, who had local control at 2 years in 54 per cent[79]

Tolerance of aggressive multimodality regimens for the treatment of locally advanced primary or recurrent rectal cancer

Although the benefits of preoperative EBRT are not debated, the attendant risk of complications deserves mention. Shumate and colleagues[46] reported on 48 patients treated with chemoradiation and described no difference in complications when this group was compared with a historical group having ERBT alone. Other authors have reported treatment-related mortality rates as high as 12 per cent[33]. Morbidity rates of between 21 and 76 per cent have also been reported with EBRT[9,13,21–31]. Preoperative radiation therapy technique may be related directly to postoperative mortality[80]. By using shaped multiple-field techniques for initial large pelvic fields and delivering 45 Gy in 25 fractions over 5 weeks, followed by a reduced boost field to the gross tumour plus 2 cm to 50–55 Gy, in combination with small bowel visualization and bladder distension, acute small bowel-related toxicity may be reduced to rates of less than 5 per cent[48,49].

The addition of chemotherapy with preoperative irradiation increases the proportion of grade 1 and 3 toxicities[29–31], although this has not been a universal finding[46]. Minsky and colleagues[31] in a non-randomized trial found that acute toxicity rates appeared to be reduced by delivering chemoradiotherapy before operation compared with postoperative delivery. The incidence of grade 3–4 toxicity with preoperative *versus* postoperative therapy was 13 and 48 per cent respectively, despite the fact that more patients in the preoperative group received a high dose of 5-FU.

IORT given in one dose does not conform to the general principle of fractionation in radiation treatment, which allows for the repair of sublethal damage to normal tissues and permits reoxygenation. Although the peripheral nerve is the principal dose-limiting structure for IORT in the pelvis, the ureter is also dose sensitive[50]. In the most recent analysis of 56 patients who received IOERT at the Mayo Clinic, the incidence of peripheral neuropathy of any degree was 33 per cent (18 patients), with a 5 per cent incidence of severe neuropathy[78]. Patients who received doses exceeding 15 Gy were most likely to suffer this complication[78]. These clinical observations have correlated closely with experimental findings[81–83]. In a previous analysis of 51 patients receiving pelvic IOERT for primary or recurrent malignancy, 44 per cent of previously unobstructed ureters became partially or totally obstructed[50]. Stent insertion, where indicated, will overcome this problem.

Finally, patient selection is crucial for the aggressive surgery that is often involved in these cases. In some patients all that is required is a completion abdominoperineal resection or pelvic exenteration to achieve negative margins. In the more extensive cases, where sacrectomy with pelvic reconstruction is required, operating times are prolonged, with significant transfusion requirements and morbidity rates. To illustrate this, Magrini and colleagues[84] reported outcome following sacropelvic resection in 16 patients for the management of recurrent rectal cancer. Median operating time was 12·5 h and median blood loss was 3350 ml. There was no perioperative mortality but there was a 50 per cent rate of major morbidity, including wound complications, urinary leak and enteric fistula formation. These rates compare favourably with those in other series, which have recorded mortality rates of approximately 7 per cent[2–6]. The requirement for a medically fit patient, who is able to tolerate the toxicity associated with preoperative chemoradiation and the sequelae of complex pelvic surgery combined with large doses of IORT, will ultimately reduce the numbers with locally advanced primary or advanced rectal cancer that are suitable for this approach.

Overview

The primary aim of all surgery for colorectal cancer is to achieve a curative resection and prevent locoregional recurrence. Unfortunately, 5–10 per cent of patients with rectal cancer will be irresectable at the time of surgery[35]. Much attention has been paid to the need to reduce local recurrence of resectable disease by the use of proper surgical technique[35–40,85]. Less emphasis has been given to improving outcome for those with irresectable disease or locoregional recurrence. The evidence discussed in this review suggests that the best results in these patients are obtained when a multimodality approach is employed, combining preoperative EBRT with chemosensitization followed by radical surgery and IORT.

The conclusions drawn from this review have not been based on controlled trial data. Randomized trials have not been feasible for a number of reasons, including small patient numbers, the complexity of surgical procedures and the lack of availability of the expensive equipment for what has been regarded as a largely experimental approach. Nevertheless, several studies have shown that combined modality therapy consistently and significantly downstages disease[30,58] and results in a superior 5-year disease-free survival rate compared with that in historical controls[19,54,75]. Early reports of improved outcome in patients with clinically irresectable disease[50,53] have recently been confirmed by several centres in Europe and the United States[47,54–61]. On the basis of a non-randomized trial from Munich, a multicentre randomized study assessing the components of this multimodality approach has been proposed[58].

Despite the stated reservations discussed above, encouraging trends exist in rectal IORT analysis with regard to improvement in local control and survival of patients with locally advanced primary and recurrent rectal cancer when compared with non-IORT series. Accordingly, continued evaluation of IORT approaches seems warranted. Disease control within the IORT and external field is diminished when gross total resection cannot be achieved surgically. Therefore, 5-FU-based chemotherapy regimens should be considered during EBRT and future clinical trials should address the role of radiation dose modifiers (sensitizers, hyperthermia) in conjunction with IORT[86].

Because the incidence of distant metastasis remains excessive in patients with locally advanced primary and recurrent rectal cancers, maintenance as well as concomitant chemotherapy should continue to be evaluated as a component of this aggressive multimodality approach. Alternative drug regimens in patients who have not received previous chemotherapy, or who have progressed despite having received it, include bolus chemotherapy with multiple drugs (5-FU, leucovorin, levamisole) or prolonged 5-FU infusion in combination with other chemotherapeutic agents in the postoperative period[29–31,45–47,50,51,87–95].

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Review

Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses

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Background Previous meta-analyses comparing low molecular weight heparin (LMWH) and unfractionated heparin for thrombosis prophylaxis after surgical interventions need updating.

Methods This is a publication-based meta-analysis of 36 double-blind studies including 16 583 patients. Main outcome measures are incidence of deep vein thrombosis (efficacy) and wound haematoma (safety).

Results In general surgery there is no increased efficacy in favour of LMWH (odds ratio (OR) 0·88, 95 per cent confidence interval (c.i.) 0·60–1·30) but there exists a higher incidence of bleeding complications (OR 1·47, 95 per cent c.i. 1·07–2·01). Low-dose LMWH is equally efficacious (OR 1·03, 95 per cent c.i. 0·85–1·26) but safer than unfractionated heparin (OR 0·68, 95 per cent c.i. 0·56–0·82). In orthopaedic surgery there is a trend towards an increased efficacy for LMWH (OR 0·83, 95 per cent c.i. 0·68–1·02) with equivalent safety (OR 0·96, 95 per cent c.i. 0·68–1·36).

Conclusion A superiority of LMWH is suggested but heterogeneity might make generalizability to future patients questionable. A meta-analysis on individual patient data should be the next step before randomizing additional patients in future trials.

Deep vein thrombosis (DVT) is a common complication after major surgical interventions. Thrombus formation in the deep veins is a consequence of surgical trauma, prolonged operative procedures and limited postoperative mobility. Known risk factors are patient age, obesity, malignancy, previous history of venous thrombosis, varicose veins, recent operative procedures and thrombophilic states[1]. The mobility of the thrombus is greatest in the first 5 days after operation and is usually considered problematic up to day 9. Some of these thrombi might travel to the lungs and lead to pulmonary embolism (PE)[2]. The positive effect of a prophylactic treatment with standard unfractionated heparin (UFH) has been investigated since the 1930s and is now beyond any doubt. Results have been summarized in three meta-analyses[2–4].

Low molecular weight heparins (LMWHs), fractions and fragments of UFH, have been under investigation since 1984. Advantages of their use in clinical medicine are increased bioavailability and plasma half-life, which enable once a day administration in comparison with two or three injections a day for UFH.

Various *in vitro* clotting and animal experiments gave rise to the expectation of a better benefit : risk ratio (i.e. prophylaxis of thromboembolic events *versus* the risk of bleeding complications) for LMWH in comparison to UFH. At least five meta-analyses have been published between 1989 and 1993 presenting available knowledge with respect to such expectation[5–9]. However, the mere fact that there is still ongoing research suggests that the evidence provided so far is not regarded as sufficient. This paper updates previous meta-analyses.

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Methods

Study protocol

A study protocol describing criteria for the inclusion and exclusion of clinical trials, the search strategy for the retrieval of trials, the main analyses and the statistical methods was specified in advance; the study protocol was agreed in November 1992.

Data collection

Search strategy. Based on the meta-analysis of one participant in this investigation (J.P.D.) pharmaceutical companies were contacted in order to locate unpublished clinical trials. Medline was scanned beginning with January 1988 and this search was regularly updated until March 1996. Embase searches covered the time-frame January 1990 to March 1996. The Medline search included 'low molecular weight heparin' as a MeSH (medical subject heading) and as free text in title or abstract. In addition, a search was made for code numbers (CY216, CY222, KABI2165, LHN1, PK10169) and trade and generic names (Clexane, Clivarin, Dalteparin, Enoxaparin, Fragmin, Fraxiparin, Innohep, Logiparin, Lovenox, Mono-Embolex NM, Nadroparin, Sandoparin and Tedelparin). Further search conditions were 'postoperative complications' with the subheading 'prevention and control', 'thromboembolism – prevention and control' and 'thrombophlebitis – prevention and control'. This search was further restricted by the mandatory criteria 'randomized clinical trials', 'clinical trial' or 'controlled clinical trials', but not 'review' or 'meta-analysis'. As further restrictions the checktag 'human' and the publication languages 'English, French, German, Italian, Spanish' were specified. The references in each publication located were checked carefully to complete the literature search. For some studies more than one publication was available. In such cases an attempt was made to extract the relevant information from all publications. All citations have been enclosed in the list of references.

Criteria for inclusion/exclusion. All randomized double-blind clinical trials comparing LMWH and UFH for prophylaxis against thromboembolic events after surgical interventions in general and orthopaedic surgery (including gynaecological, urological and malignant disease operations) were selected. Studies including additions of dihydroergotamine (DHE) were eligible only if DHE was added to both treatment arms. Studies investigating Organon, a heparinoid, were not included. No restrictions were made with respect to the methods used for the detection of DVT.

Extracted information. Data have been extracted by two persons independently (A.K., S.B.). Conflicting findings were resolved in a meeting with all participants of this working group.

Endpoints. Based on sample size considerations an initial decision was made to use the endpoints DVT and wound haematoma (WH) for the definite comparison of safety and efficacy of the two treatments. In cases where results of more than one diagnostic test were available (e.g. radiofibrinogen uptake test and phlebography) the results of the method regarded to be most reliable have been used for the main analysis. Analyses for other endpoints are presented, but as study publications provided information on a variety of variables, none of which was available from all publications, these analyses are always restricted to subsets of the study population.

Statistical methods

For all analyses the results of the single trials have been summarized in fourfold tables for each endpoint under investigation. Odds ratios and 95 per cent confidence intervals have been computed to estimate the effect of LMWH in comparison to UFH. An odds ratio equal to 1 indicates no difference between LMWH and UFH. The odds ratio is less than 1 if a smaller event rate under a treatment with LMWH has been observed, which indicates in general a superiority of LMWH in comparison to UFH (e.g. fewer thromboses or fewer bleeding complications were observed under LMWH). Mantel-Haenszel estimates[10] for the odds ratio with respective 95 per cent confidence intervals are presented in the meta-analysis. *P* values are presented in addition to guide the reader in the evaluation of results. One treatment was considered superior to the other if the confidence interval did not include 1. Non-informative studies (i.e. in both treatment arms no events were observed) do not influence the Mantel–Haenszel estimate.

For the investigation of heterogeneity (i.e. second order interactions between studies and treatments) the Breslow–Day test was performed. The test statistic follows a χ^2 distribution under the null hypothesis of homogeneous effects. The number of degrees of freedom (d.f.) equals the number of trials included minus 1, minus the number of non-informative studies. Heterogeneity was considered important if the corresponding *P* value was less than 0·20, a value specified in advance in the study protocol. In this situation the generalizability of results on future patients is doubtful. Thompson[11] has proposed that the contribution of the single trials to the heterogeneity statistics should be investigated. These contributions are termed 'major' if statistically significant compared with a χ^2 distribution with 1 d.f. For the main analyses these studies have been identified. For all main analyses the study with greatest relative weight (that is most influential on the summary estimate) is identified[11].

Main analyses were investigation of all studies, subgroup analyses for studies in general surgery (with separation into low-dose (3400 units or less) and high-dose (more than 3400 units) studies), and orthopaedic surgery. In instances of formal significance of a treatment effect in these analyses the odds ratio in the random effects model[12] has been presented as a type of sensitivity analysis[13] in order to demonstrate stability of results in the presence of heterogeneity. Further sensitivity analyses were (1) restriction of the analysis to number of patients diagnosed with DVT, which is sometimes not equal to the number of patients initially randomized to the two treatments, (2) investigation of the effect of different diagnostic tests for the assessment of DVT on the estimation of a treatment effect, and (3) a safety analysis imputing other bleeding complications when WH was not reported. Additional analyses for differences between different diagnostic methods and various endpoints for the evaluation of the safety profile are presented descriptively.

All analyses were planned to be performed on an intention to treat basis, i.e. the denominator of event rates was intended to be the number of patients randomized to the two treatment arms. Analyses have been carried out using SAS version 6·09 on an HP-UX 7000/900 workstation.

Results

Located studies

A total of 36 double-blind clinical trials were found. Two studies were unpublished (Maroske, 1985; Koppenhagen *et al.*, 1990) and were located by direct contact with pharmaceutical companies. Twenty-five studies investigated surgical interventions in general surgery and there were 11 studies in orthopaedic surgery. Fourteen publications reported on findings from multicentre clinical trials[14–27].

Table 1 presents the main characteristics of the double-blind clinical trials included. The list is sorted by publication year. Two studies included two different dosages of LMWH[22,29]. Two additional trials included an additional placebo arm, which has been excluded and is not displayed[18,19]. The study of Koller *et al.*[31] was terminated early because of an unexpectedly high number of bleeding complications and initiated again later with a lower dose of LMWH. For the first study only numbers of bleeding complications were presented. For the analysis it is assumed that no DVT occurred. The majority of studies investigated a single daily injection of LMWH compared with one placebo injection. Nine studies administered three daily injections of UFH and performed two placebo injections[24,25,27,38,42,44,46,51,62]. Two studies[23,29] used a regimen with two LMWH injections a day. This meta-analysis

Table 1 Main characteristics of clinical trials included

Reference	Year	Type of surgery	Dose (units)*	Product	Diagnosis	Deep vein thrombosis		Wound haematoma		Total deaths		Pulmonary embolism		Injection site haematoma		Postoperative bleeding requiring transfusion		Postoperative bleeding requiring reintervention		Postoperative bleeding requiring withdrawal	
						LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH
Schmitz-Huebner *et al*[29]	1984	Gen.	10 400	Mono-Embolex	RUT	3/41	0/42	7/41	8/42	—	—	—	—	6/41	8/42	—	—	—	—	2/41	0/42
			13 600	Mono-Embolex	RUT	0/43	—	10/43	—	—	—	—	—	9/43	—	—	—	—	—	9/43	—
Kakkar and Murray[14]	1985	Gen.	3 400	Fraxiparin	RUT	5/196	15/199	11/196	14/199	5/196	5/199	0/196	1/199	—	—	—	—	—	—	3/196	6/199
Maroske‡	1985	Orth	3 100	Embolex†	CLSv	7/40	7/40	—	—	0/40	0/40	—	—	—	—	10/40	12/40	0/40	0/40	—	—
Bergqvist *et al*[15,30]	1986	Gen	5 000	Fragmin	RUT	13/215	9/217	13/215	7/217	5/215	5/217	0/215	1/217	72/215	96/217	75/215	55/217	10/215	2/217	—	—
Koller *et al*[31]	1986	Gen	7 500	Fragmin	RUTv	—	—	7/23	2/20	0/23	0/20	—	—	—	—	—	—	—	—	6/23	1/20
Koller *et al.*[31]	1986	Gen.	2 500	Fragmin	RUTv	2/75	1/75	3/75	2/75	0/75	0/75	—	—	1/75	0/75	—	—	0/75	0/75	5/75	2/75
Onarheim *et al*[32]	1986	Gen	5 000	Fragmin	RUTv	1/25	0/27	0/25	1/27	0/25	0/27	0/25	0/27	—	—	—	—	1/25	0/27	0/25	1/27
Sasahara *et al*[33]	1986	Gen	3 100	Embolex†	RUT	14/137	13/132	4/137	3/132	2/137	5/132	0/137	0/132	—	—	19/137	31/132	—	—	—	—
Voigt *et al*[34]	1986	Gen	3 100	Embolex†	CLSv	1/103	1/97	29/103	24/97	4/103	6/97	0/103	1/97	48/103	48/97	55/103	57/97	3/103	1/97	—	—
Haas *et al*[35]	1987	Orth.	3 100	Embolex†	RUT	15/80	15/80	21/80	21/80	0/80	0/80	0/80	1/80	4/80	9/80	—	—	—	—	—	—
Bergqvist *et al*[16,36]	1988, 1990	Gen.	5 000	Fragmin	RUT	28/505	41/497	25/505	10/497	10/505	10/497	0/505	5/497	36/505	47/497	—	—	31/505	27/497	—	—
Borstad *et al*[37]	1988	Gen	5 000	Fragmin	CLSv or IPLv	0/105	0/110	26/105	15/110	—	—	0/105	0/110	—	—	—	—	1/105	1/110	4/105	1/110
Caen[17]	1988	Gen	2 500	Fragmin	RUT	6/190	7/195	4/190	3/195	2/190	3/195	0/190	0/195	—	—	11/190	8/195	—	—	—	—
Lassen *et al*[18]	1988	Orth	3 100	Embolex†	RUTv	35/118	34/122	0/118	0/122	0/118	0/122	—	—	33/118	42/122	96/118	98/122	—	—	—	—
Planes *et al*[21,38–41]	1988, 1990	Orth	4 000	Enoxaparin	PHL	15/124	27/113	8/124	5/113	0/124	0/113	0/124	1/113	—	—	45/124	52/113	1/124	1/113	—	—
Adolf *et al*[42]	1989	Gen.	3 100	Mono-Embolex	RUT	25/205	24/205	14/205	19/205	—	—	—	—	33/205	58/205	63/205	48/205	—	—	—	—
Baumgartner *et al*[43]	1989	Gen	3 100	Embolex†	RUTv	6/99	7/102	1/99	0/102	1/99	2/102	1/99	1/102	23/99	20/102	—	—	—	—	0/99	0/102
Heilmann *et al*[44]	1989	Gen.	3 100	Mono-Embolex	IPLv	2/150	6/150	19/150	27/150	—	—	0/150	0/150	—	—	—	—	2/150	3/150	—	—
Kakkar *et al*[45]	1989	Gen.	3 100	Embolex†	RUTv	8/88	10/91	2/88	1/91	—	—	2/88	0/91	—	—	—	—	—	—	—	—
Lassen *et al*[19]	1989	Orth	3 100	Embolex†	RUTv	14/68	23/71	—	—	4/68	2/71	1/68	0/71	9/68	14/71	—	—	—	—	—	—
Monreal *et al*[46]	1989	Orth	5 000	Fragmin	RUTv or PHL	14/46	6/44	2/46	2/44	2/46	3/44	6/46	0/44	—	—	—	—	—	—	—	—
Reilmann *et al*[47]	1989	Orth.	3 100	Embolex†	RUTv	8/68	6/71	15/68	17/71	—	—	1/68	2/71	—	—	—	—	1/68	3/71	—	—
Hartl *et al*[48]	1990	Gen.	2 500	Fragmin	RUTv	5/126	5/124	1/126	1/124	—	—	—	—	—	—	2/126	9/124	1/126	3/124	—	—
Hoffmann *et al*[49,50]	1990, 1992	Gen.	3 000	Mono-Embolex	LCCv	1/298	3/296	—	—	—	—	1/298	1/296	—	—	—	—	10/298	7/296	—	—

Table 1–*Continued*

Reference	Year	Type of surgery	Dose (units)*	Product	Diagnosis	Deep vein thrombosis		Wound haematoma		Total deaths		Pulmonary embolism		Injection site haematoma		Postoperative bleeding requiring transfusion		Postoperative bleeding requiring reintervention		Postoperative bleeding requiring withdrawal	
						LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH
Koppenhagen *et al* ‡	1990	Gen	3 100	Mono-Embolex	RUTv	4/51	7/53	0/51	0/53	0/51	0/53	—	—	1/51	0/53	—	—	0/51	0/53	—	—
Koppenhagen *et al* ‡	1990	Gen	2 500	Clivarin	RUTv	2/42	4/42	6/42	2/42	0/42	0/42	0/42	0/42	13/42	9/42	—	—	—	—	—	—
Eriksson *et al*[51]	1991	Orth	5 000	Fragmin	PHL	19/67	25/69	0/67	0/69	0/67	1/69	8/67	19/69	2/67	7/69	—	—	0/67	0/69	—	—
Freick and Haas[52]	1991	Orth.	3 100	Embolex†	PHL	5/55	12/55	1/55	1/55	—	—	0/55	1/55	—	—	20/55	27/55	—	—	—	—
Leizorovicz *et al*[22,53]	1991,	Gen.	2 500	Logiparin	RUTv	16/431	7/429	5/431	28/429	10/431	9/429	—	—	5/431	28/429	—	—	14/431	13/429	0/431	1/429
	1993		3 500	Logiparin	RUTv	7/430	—	21/430	—	10/430	—	—	—	21/430	—	—	—	14/430	—	1/430	—
Levine *et al*[23]	1991	Orth.	4 800	Enoxaparin	PHL	50/333	61/332	—	—	0/333	0/332	—	—	—	—	—	—	—	—	—	—
Borstad *et al*[54]	1992	Gen	2 500	Fragmin	CLSv	0/77	0/75	5/77	11/75	2/77	0/75	—	—	—	—	—	—	—	—	1/77	1/75
GHAT[24]	1992	Orth	4 700	Fraxiparin	PHL	45/169	47/172	32/169	36/172	0/169	3/172	2/169	6/172	—	—	33/169	37/172	1/169	1/172	—	—
Koppenhagen *et al*[25]	1992	Gen	3 100	Mono-Embolex	RUT	27/323	27/330	2/323	0/330	2/323	3/330	0/323	3/330	16/323	21/330	7/323	13/330	—	—	—	—
Boneu[20]	1993	Gen	1 750	Clivarin	RUTv	30/672	29/679	55/672	80/679	—	—	1/672	3/679	11/672	31/679	—	—	—	—	—	—
Kakkar *et al.*[26]	1993	Gen	2 500	Fragmin	CLSv	6/1960	6/1978	27/1960	52/1978	63/1960	47/1978	19/1960	22/1978	74/1960	120/1978	59/1960	59/1978	20/1960	38/1978	36/1960	40/1978
Nurmohamed *et al*[27,55]	1994, 1995	Gen	2 000	Enoxaparin	RUT	54/737	37/734	—	—	4/737	6/734	—	—	—	—	71/737	81/734	4/737	13/734	—	—

*Anti-Xa units. †Supplementary treatment with dihydroergotamine in both treatment groups ‡Unpublished results LMWH, low molecular weight heparin; UFH, unfractionated heparin; Gen., general, Orth , orthopaedic, RUT, radiofibrinogen uptake test, CLS, clinical symptoms, IPL, impedance plethysmography, PHL, phlebography, LCC, liquid crystal contact thermography; v, verified by PHL, GHAT, German Hip Arthroplasty Trial includes results on a total of 16 583 patients. A funnel plot (*Fig. 1*) provides some descriptive evidence for the absence of publication bias.

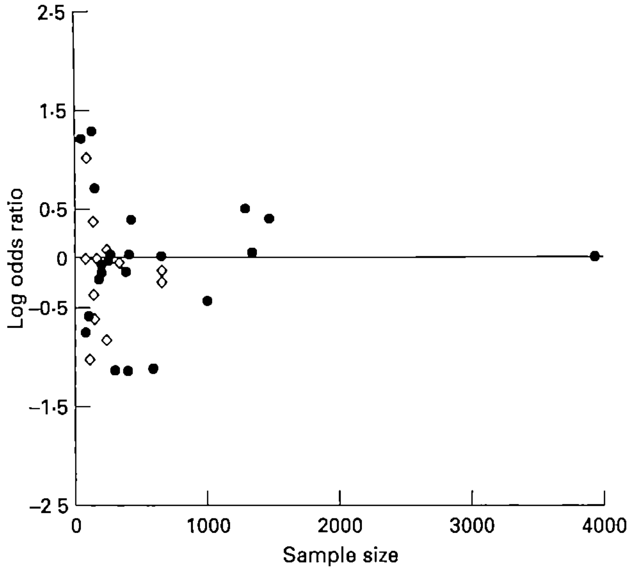

Fig. 1 Funnel plot (the logarithm of the odds ratio is less than zero if the incidence of deep vein thrombosis is smaller in the low molecular weight heparin group) ●, general surgery; ◇, orthopaedic surgery

Available information

When extracting information from the study publications the availability of 29 relevant parameters for the description of efficacy and safety in the included trials, and the risk profile of the patient populations, was checked. *Fig. 2* presents the results. Five publications did not provide the exact numbers of patients randomized to the two treatment arms[15,34,45,49,51]. Thus an analysis on an intention to treat basis was not possible without further assumptions. For one study[49] the number of patients randomized could be derived from information provided. For the five other studies the number of patients treated with LMWH and UFH was estimated. The only parameter consistently documented for the description of the patient population was mean age. A large variety of parameters has been used to describe the safety profile of the two treatments, none of which has been presented in all of the study publications.

Main analysis of all studies

Two of the 36 double-blind clinical trials presented significant treatment effects with respect to efficacy[21,29] and five studies with respect to safety[16,20,22,26,37]. All results of the main efficacy and safety analyses are summarized in *Table 2*. The combined evaluation of studies in general and orthopaedic surgery showed a non-significant reduction in the rate of DVT (odds ratio 0·92, $P=0{\cdot}19$). There is no indication of heterogeneity ($\chi^2=37{\cdot}7$, 32 d.f., $P=0{\cdot}23$). Four studies made major contributions to the heterogeneity statistics[14,21,27,46]. Most influential on the meta-analysis estimate is the study of Levine *et al.*[23] with a weight of approximately 10 per cent. Five studies did not provide results on WH and were thus not included in the main safety analysis. There is a non-significant trend towards a better safety profile for LMWH (odds ratio 0·88, $P=0{\cdot}10$). Study effects were, however, heterogeneous ($\chi^2=47{\cdot}7$, 27 d.f., $P<0{\cdot}01$). Four studies made major contributions to the heterogeneity statistics[16,22,26,37]. Greatest weight is attributed to the study of Boneu[20] (20 per cent).

Subgroup analyses for studies in general surgery

Efficacy. Because of heterogeneity with respect to safety results, separate analyses for studies in general and in orthopaedic surgery were necessary. In general surgery LMWH and UFH can be assumed to be equivalent with respect to efficacy (odds ratio 0·99, $P=0{\cdot}88$). There is no indication of heterogeneity of effects ($\chi^2=21{\cdot}3$, 21 d.f., $P=0{\cdot}44$) and only the study of Kakkar and Murray[14] contributed significantly to the heterogeneity statistics. Approximately equal weights are attributed to the studies of Bergqvist *et al.*[16] (16 per cent) and Nurmohamed *et al.*[27] (14 per cent).

Safety. Fewer WHs were observed under a treatment with LMWH in the subgroup of studies in general surgery (odds ratio 0·86, $P=0{\cdot}09$). This step did, however, not reduce heterogeneity ($\chi^2=46{\cdot}7$, 21 d.f., $P<0{\cdot}01$). Major contributions to the heterogeneity statistics came from four studies[16,22,26,37]; greatest weight is given to the low-dose study of Boneu[20]. To investigate this heterogeneity further, separate analyses have been performed for studies with high-dose and low-dose LMWH regimens. Because of the cut-off point of 3400 units in the two treatment arms in the study of Leizorovicz *et al.*[22], this study now contributes to different analyses and was counted as two separate studies. No adjustment was performed for counting the respective control groups twice.

High-dose studies. Analysis of seven studies does not support the hypothesis of increased efficacy of high-dose prophylaxis with LMWH (odds ratio 0·88, $P=0{\cdot}53$). Homogeneity of study results can be assumed ($\chi^2=5{\cdot}9$, 4 d.f., $P=0{\cdot}21$). Moreover, the safety analysis indicates a clear superiority of treatment with UFH (odds ratio 1·47, $P=0{\cdot}02$). Study results were not homogeneous ($\chi^2=12{\cdot}0$, 6 d.f., $P=0{\cdot}06$). The high-dose arm in the study of Leizorovicz *et al.*[22] has greatest weight (41 per cent) and also contributes significantly to heterogeneity.

Low-dose studies. Results from 19 studies demonstrate equivalence of a low-dose regimen of LMWH and UFH (odds ratio 1·03, $P=0{\cdot}76$) with respect to efficacy. There is no indication of heterogeneity of effects ($\chi^2=17{\cdot}2$, 17 d.f., $P=0{\cdot}44$). In this subgroup the safety analysis (odds ratio 0·68, $P<0{\cdot}01$) indicates a clear advantage of treatment with LMWH. Study results were not homogeneous ($\chi^2=26{\cdot}9$, 15 d.f., $P=0{\cdot}03$). Major contributions to heterogeneity came from the studies of Leizorovicz *et al.*[22] and Koppenhagen *et al.* (unpublished results). The study of Boneu[20] has the greatest weight (30 per cent).

Subgroup analysis for studies in orthopaedic surgery

Efficacy results in orthopaedic surgery are in favour of LMWH (odds ratio 0·83, $P=0{\cdot}07$). The heterogeneity test is significant according to the prespecified level ($\chi^2=14{\cdot}9$, 10 d.f., $P=0{\cdot}14$). The study of Monreal *et al.*[46] had a major contribution to heterogeneity. Greatest weight (25 per cent) is given to the study of Levine *et al.*[23] Only eight studies were available for the safety analysis. The odds ratio is 0·96 ($P = 0{\cdot}83$) and there is no indication for heterogeneity of estimated treatment effects ($\chi^2 = 0{\cdot}7$, 5 d.f., $P = 0{\cdot}98$). Greatest weight is given to the German Hip Arthroplasty Trial[24] with approximately 44 per cent.

Sensitivity analyses

Random effects approach. Two treatment effects achieved formal or borderline significance in the meta-analysis in favour of treatment with LMWH: in orthopaedic surgery a treatment with LMWH was superior with respect to efficacy. For these studies the random effects odds ratio was similar to computations in the fixed effects approach (DerSimonian and Laird estimate for the odds ratio is 0·83, confidence interval 0·64–1·08, $P = 0{\cdot}17$). The treatment effect is, however, no longer borderline statistically significant, indicating a non-negligible influence of heterogeneity on efficacy results. In general surgery, safety was increased in low-dose LMWH studies. The corresponding random effects estimate is slightly more conservative but still indicating a clear superiority of a treatment with LMWH (DerSimonian and Laird estimate for the odds ratio is 0·72, confidence interval 0·54–0·97, $P = 0{\cdot}03$).

Loss of patients. In some studies the number of patients diagnosed for DVT was less than the number of patients randomized to the two treatment arms. Reasons such as 'angiogram not available' or 'incorrect thyroid blocking' are acceptable for the present situation of a blind assessment of the endpoint. In a second sensitivity analysis, event numbers were related to the number of patients diagnosed. This did not change the efficacy results: for all types of surgical intervention 493 of 8186 (6·0 per cent) had DVT in the LMWH group and 522 of 7728 (6·8 per cent) in the UFH group. The odds ratio in this analysis was 0·91 (confidence interval 0·79–1·04, $P = 0{\cdot}15$). In the subgroups of studies in general surgery and in orthopaedic surgery the odds ratios were 0·99 and 0·81 respectively. Results agree well with the main analysis.

Diagnostic methods. More than nine diagnostic tests and strategies have been used in the 36 clinical trials. Eleven publications (Maroske, unpublished results)[22,24,26,32,34,43,45,47,48,54] provided results of a screening test

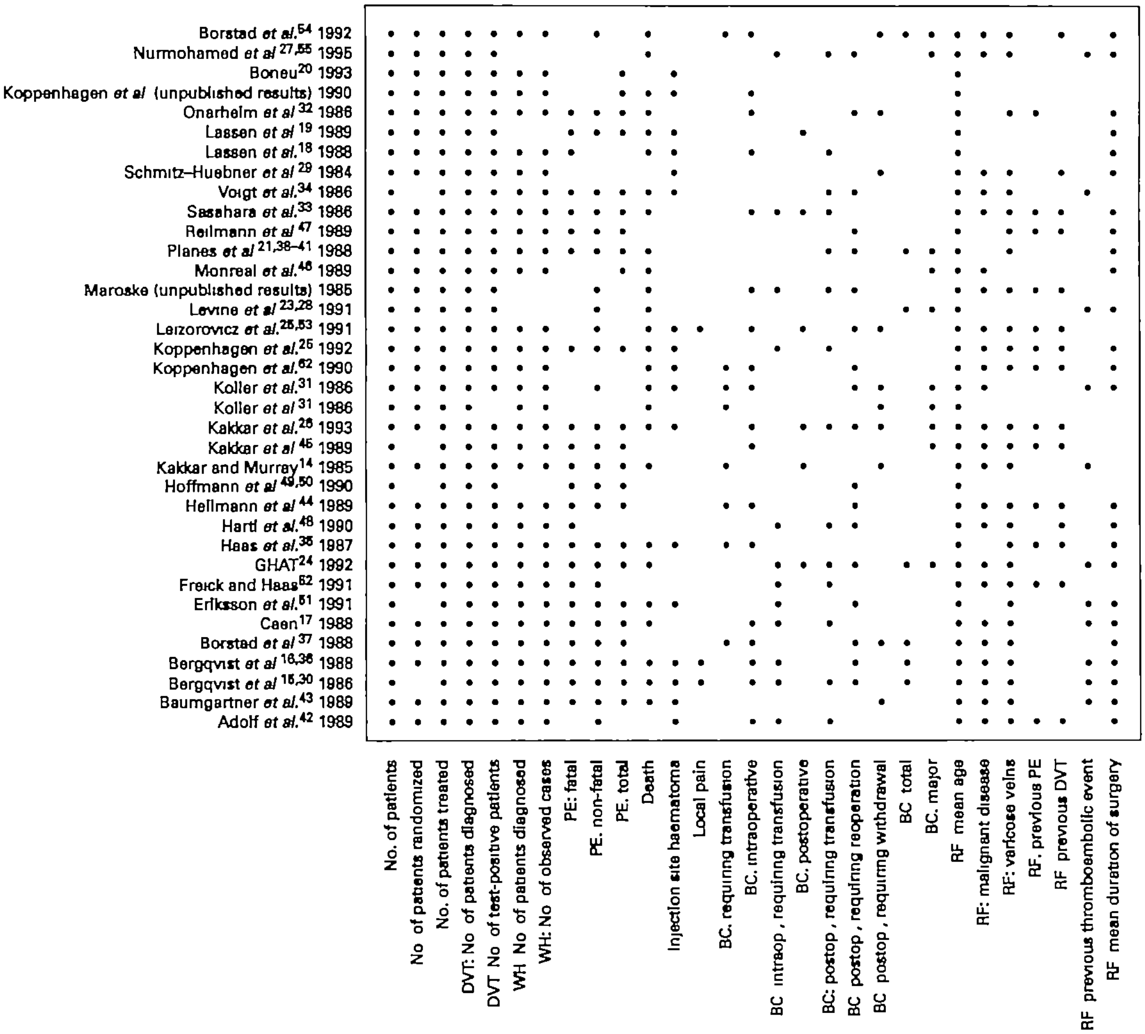

Fig. 2 Availability of 29 key parameters in publications studied. PE, pulmonary embolism; BC, bleeding complications; RF, risk factor; WH, wound haematoma; DVT, deep vein thrombosis

Table 2 Summary of results of the main analyses

	Efficacy analysis					Safety analysis				
		Proportion of DVT*					Proportion of WH			
	Studies	LMWH	UFH	Odds ratio†	Heterogeneity	Studies	LMWH	UFH	Odds ratio†	Heterogeneity
All studies	36	493/8515 (5·8)	522/8068 (6·5)	0·92 (0·80–1·05)	0·23	31	376/7039 (5·3)	392/6595 (5·9)	0·88 (0·76–1·03)	0·008
General surgery	25	266/7347 (3·6)	259/6899 (3·8)	0·99 (0·83–1·18)	0·44	23	297/6312 (4·7)	310/5869 (5·3)	0·86 (0·73–1·02)	0·001
Orthopaedic surgery	11	227/1168 (19·4)	263/1169 (22·5)	0·83 (0·68–1·02)	0·14	8	79/727 (10·9)	82/726 (11·3)	0·96 (0·68–1·36)	0·98
General surgery (low-dose)	19	214/5960 (3·6)	209/5986 (3·5)	1·03 (0·85–1·26)	0·44	17	188/4925 (3·8)	267/4956 (5·4)	0·68 (0·56–0·82)	0·03
General surgery (high dose)	7	52/1387 (3·7)	57/1342 (4·2)	0·88 (0·60–1·30)	0·21	7	109/1387 (7·9)	71/1342 (5·3)	1·47 (1·07–2·01)	0·06

Values in parentheses are *percentages or †95 per cent confidence interval. DVT, deep venous thrombosis; WH, wound haematoma; LMWH, low molecular weight heparin, UFH, unfractionated heparin

(diagnosis of clinical symptoms or radiofibrinogen uptake test) and of a test strategy confirming positive results of the screening test with phlebography. Results on a total of 6822 patients in general and orthopaedic surgery are available. These were used to assess the role of different diagnostic procedures on the estimation of a treatment effect. For the screening tests 117 of 3616 (3·2 per cent) events in LMWH-treated patients and 90 of 3206 (2·8 per cent) events in UFH-treated patients were registered. The odds ratio is 1·08 (confidence interval 0·80–1·46, $P=0{\cdot}61$). There is no indication of heterogeneity of treatment effects ($\chi^2=5{\cdot}6$, 9 d.f., $P=0{\cdot}78$). Considering the results of the diagnostic test procedure, confirming positive results of the screening test with phlebography, event rates are 66 of 3616 (1·8 per cent) in the LMWH group and 54 of 3206 (1·7 per cent) in the UFH group. The odds ratio is 1·05 (confidence interval 0·72–1·54, $P=0{\cdot}79$). Both analyses lead to very similar results.

Safety results. The main safety analysis in orthopaedic surgery involves only 1453 of 2337 patients (62·1 per cent). None of the safety parameters is documented more completely than WH. To present a safety analysis including results from all studies the following endpoints were utilized for the studies which did not report WH: total bleeding complications[23], postoperative bleeding leading to transfusion (Maroske, unpublished results), and injection site haematoma[19]. The event rates were 115 of 1168 (9·8 per cent) in the LMWH group and 139 of 1169 (11·9 per cent) in the UFH group. Contrary to the main analysis, an odds ratio of 0·80 (confidence interval 0·61–1·05, $P=0{\cdot}11$) was found, indicating a superiority of LMWH over UFH; heterogeneity was still not significant ($\chi^2=4{\cdot}0$, 8 d.f., $P=0{\cdot}86$).

Additional analyses

The following section summarizes the results using six additional parameters for the description of efficacy and safety. Results of the individual studies are reported in *Table 1* and summarized in *Table 3*. Whenever possible, event numbers are reported as fractions of the number of patients initially randomized to treatment. If this was not possible, the number of patients treated with LMWH and UFH has been used.

Table 3 Summary of additional analyses

	No of studies	Proportion of events*		Odds ratio†	*P* (heterogeneity)
		LMWH	UFH		
Total deaths	26	126/6664 (1·9)	110/6245 (1·8)	1·06 (0·82–1·37)	0·64
Pulmonary embolism	24	42/5785 (0·7)	68/5817 (1·2)	0·61 (0·41–0·90)	0·05
Injection site haematoma	17	417/5528 (7·5)	558/5088 (11·0)	0·65 (0·56–0·75)	0·17
Postoperative bleeding requiring withdrawal	10	67/3505 (1·9)	53/3057 (1·7)	1·19 (0·82–1·72)	0·06
Postoperative bleeding requiring reoperation	18	114/5679 (2·0)	113/5252 (2·2)	0·89 (0·68–1·16)	0·09
Postoperative bleeding requiring transfusion	14	566/4502 (12·6)	587/4514 (13·0)	0·94 (0·81–1·08)	0·03

Values in parentheses are *percentages or †confidence intervals LMWH, low molecular weight heparin, UFH, unfractionated heparin

Only 26 of the studies reported the number of deaths during the course of the trial. The corresponding analysis shows no difference between a treatment with LMWH and one with UFH. Equally, there is no indication of superiority of one treatment with respect to the following parameters: the number of postoperative bleeding complications requiring withdrawal or discontinuation of treatment, number of reoperations resulting from postoperative bleeding complications, and the number of patients needing transfusion because of postoperative bleeding. On the other hand, for PE and injection site haematoma, a superiority of LMWH over UFH was observed.

Twenty-four studies presented observed numbers of PEs. In general, the total number of PEs was analysed. When fatal and non-fatal PEs were reported, these numbers were combined. The analysis (odds ratio 0·61, $P=0\cdot01$) indicates superiority of treatment with LMWH. Study results were not homogeneous ($\chi^2=27\cdot3$, 17 d.f., $P=0\cdot05$). Injection site haematomas were reported in 17 studies. A clear superiority of treatment with LMWH can be demonstrated (odds ratio 0·65, $P<0\cdot01$). Study results were not homogeneous ($\chi^2=21\cdot2$, 16 d.f., $P=0\cdot17$).

Discussion

More than 50 clinical trials have compared LMWH and UFH for prophylaxis against thromboembolic events after major surgical intervention. Results have been summarized in at least five meta-analyses, but conclusions often remain vague and some are contradictory. An initial decision was made to restrict this analysis to double-blind clinical trials. Kakkar[9] has pointed out that open and single-blind clinical trials lead to overoptimistic estimates of the treatment effect. Some recent papers highlight doubt about sensitivity and specificity of the radiofibrinogen uptake test[56,57]. A potential cause for this is the subjective element in the assessment of results. To obtain a best evidence synthesis[58], it is advisable to adhere to the gold standard for treatment comparisons.

The authors believe that in the field of prophylaxis against thromboembolic events the restriction to double-blind studies is, in general, a sufficient criterion which guarantees a basic quality of studies and so none of the retrieved trials was excluded from this analysis. In addition, one must realize that it is not possible to distinguish between the quality of a publication and the quality of the study (e.g. well designed and conducted studies might be published with poor quality), even though some correlation certainly exists. To give the reader a general impression of the publication quality and the comparability of results in the publications under consideration, 29 parameters were selected and their availability was checked. The first rather astonishing fact is that the only consistently documented parameter for the description of the risk profile is the mean age. A second outstanding feature is the variety of parameters selected for the description of safety. Although additional information (e.g. mean volume of blood transfusion) has sometimes been presented, virtually no parameter is available in all of the study publications. This is even more remarkable as the comparison of LMWH and UFH is not the first approach to thrombosis prophylaxis research by the surgical community. In 1988 Collins *et al.*[2] stated that for studies comparing UFH and placebo 'the reporting on bleeding complications was heterogeneous and incomplete' and so some influence of this on future publications was expected. Meta-analyses are sometimes accused of being oversimplistic. One reason might be the inconsistency of presentation of primary results, which makes the introduction of assumptions necessary if all studies are to be incorporated into the meta-analysis.

Publication bias, that is the probability of a clinical trial being published depending on the significance of its results, is the major problem in meta-analysis. If publication bias is present, meta-analyses will always reach overoptimistic estimates of the treatment effect[59]. Although there is no guarantee of the absence of publication bias in the present meta-analysis, the symmetry of the funnel plot presented (*Fig. 1*) shows the expected random scatter of small clinical trials. Moreover, the number of trials which have been published describing results with respect to efficacy that were contradictory to the expectations that had led to the initiation of the trial (i.e. UFH was superior to LMWH) is not negligible.

Following the proposal of Kakkar[9], low-dose and high-dose studies in general surgery were analysed separately and the conclusions reached in his meta-analysis can be confirmed. Formal significance has been calculated for findings which previously could only be seen as trends. High-dose LMWH does not result in a lower incidence of DVT than low-dose, whereas the risk of WH is considerably increased. Low-dose LMWH provides an equal efficacy in terms of DVT, but with improved safety. This indicates that a low-dose regimen for LMWH is the more promising concept in general surgery. One has, however, to remember that results from meta-analyses do not have the same quality as results from large multicentre clinical trials. Meta-analyses are observational[60] in design, so their *P* values do not have the same interpretation as those of multicentre clinical trials. Contributing studies have been performed at different points in time and follow, at best, a similar (but not the same) study protocol. In this they incorporate the process of treatment development and minor changes in criteria for the inclusion or exclusion of patients from treatment.

On the other hand, results from a meta-analysis based on double-blind clinical trials provide better evidence than a large observational study, in which the decision about treatment is made by the physician. The same is true for meta-analyses which include open or single-blind clinical trials in which, as has been demonstrated, the evaluation of endpoints might be biased. The crucial point is the vast heterogeneity of treatment effects not documented in most previous meta-analyses. Subgroup analyses reduced heterogeneity but did not lead to homogeneous effects across the trials. As has been pointed out, this makes it even more questionable to which population the results can be generalized[61].

In orthopaedic surgery the safety profile of LMWH and UFH was similar, whereas LMWH was superior to UFH with respect to efficacy. As the basic risk of a thromboembolic event is higher in orthopaedic surgery than in general surgery, the question is raised whether the treatment effect also depends on this basic risk and whether the benefit of treatment with LMWH is greater in high-risk patients. It is worth stating that publication-based meta-analyses can only identify high-risk studies, not high-risk patients.

Sensitivity analyses did not, in general, markedly change the estimated treatment effects, except for studies in orthopaedic surgery. There, using other parameters for the description of bleeding complications strongly raises the number of patients who can be included in the safety analysis. In this analysis, a benefit of a treatment with LMWH can be seen.

Other potential sources of heterogeneity are known; studies differed with respect to a preoperative or postoperative commencement of treatment. The duration of medication and follow-up was different in the studies under investigation. Very often only information on a mean duration of treatment was available. This might influence estimated effects, but this feature cannot be addressed in a meta-analysis owing to the large number of parameters which would need to be incorporated into the analysis. In consequence, there is no wisdom in performing further publication-based meta-analyses.

Because of the dependence on results published already, future analyses would need to cope with the same limitations, which are a consequence of restricted available information in the publications studied.

In conclusion, the results of this analysis of general surgical patients are in agreement with those of Kakkar[9]; low-dose LMWH and UFH were equally efficacious while low-dose LMWH provided increased safety over UFH. High-dose LMWH in general surgery did not improve the efficacy of treatment, while safety is strongly decreased. Owing to strong heterogeneity, the generalization of these results to future patients is questionable. In studies in orthopaedic surgery LMWH provides an increase in efficacy over UFH, while preserving at least an equal safety profile. With respect to the efficacy analysis, heterogeneity was of even greater importance in this type of surgery. There is, in our opinion, no argument in favour of initiating a new and even larger clinical trial, as has been proposed by others[6]. Up to now not all available information has been used adequately. A reanalysis of the pooled individual patient data should help to identify subgroups of patients who will profit best from treatment with LMWH and diminish heterogeneity. This should be the next step in research, before considering randomizing additional patients.

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Review

High-grade dysplasia in Barrett's oesophagus

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Background The management of high-grade dysplasia (HGD) in Barrett's oesophagus is a controversial and challenging problem.

Methods An up-to-date review of the literature has been made using Index Medicus, the Medline database, and cross-referencing of major articles on this subject.

Results Diagnosis should be confirmed by a second expert pathologist. Repeat multiple jumbo biopsies and brushings need to be taken to reduce sample error and exclude associated invasive cancer. In young fit patients the advantages of surgery outweigh the disadvantage of missing an early adenocarcinoma. Continued endoscopic surveillance may be more appropriate in elderly patients. New technology has increased the number of options. Early results of laser and multipolar electrocoagulation ablation of Barrett's epithelium are encouraging. Photodynamic therapy appears to be ideally suited to HGD and early cancers

Conclusion A selective approach to the management of HGD on an individual patient basis should be adopted.

The incidence of oesophageal adenocarcinoma has been rising more rapidly over the past decade than that of any other solid tumour[1–3] Patients usually present with advanced disease with a 5-year survival rate of 5–10 per cent[4–6]. However, this figure rises to over 50 per cent for early-stage lymph node-negative disease[7] and 80 per cent for high-grade dysplasia/carcinoma *in situ* or T_1 disease[8] following oesophagectomy. Since 64–100 per cent of these cancers arise in Barrett's oesophagus[9–11], endoscopic surveillance of Barrett's oesophagus has been undertaken to identify early-stage oesophageal adenocarcinoma[12,13]. This is a highly controversial issue since there is little evidence to show that surveillance is cost-effective.

The identification of high-risk patients depends on histological assessment of the severity of dysplasia, but management of the patient with dysplasia in Barrett's oesophagus presents many problems. What is meant by dysplasia? How often should endoscopy be repeated? Is an unsuspected cancer being missed? What is the natural history of dysplasia? Does dysplasia regress? Can dysplasia be treated without open surgery?

Classification of dysplasia

The classification of dysplasia in Barrett's oesophagus has evolved over the past 20 years. In the 1970s it was recognized that Barrett's oesophagus was a premalignant condition, but the current practice of performing multiple endoscopic biopsies for surveillance purposes has been introduced relatively recently. The classifications of dysplasia in Barrett's oesophagus are adaptations of those used elsewhere in the gastrointestinal tract. The three-tiered classification of mild, moderate and severe dysplasia (as used for gastric dysplasia[14]) has been used mainly in Europe, but this is now being superseded by a more simplified (but clinically more applicable) version adapted from Riddell's classification of dysplasia in ulcerative colitis[15].

Three major categories are described: negative, indefinite, and positive for dysplasia. The indefinite category was introduced because of the difficulties in distinguishing between regenerative/inflammatory changes and low-grade dysplasia (LGD). Inflammatory changes tend to have less nuclear pleomorphism, there is less nuclear stratification and the cells resemble each other[16]. The positive for dysplasia category is divided into low (or mild) and high (or severe) grade, depending on the extent of the cytological and architectural changes; the moderate grade has been abolished to eliminate uncertainty in patient management.

Using the Riddell classification as a guideline, Reid *et al.*[17] found that there was still considerable interobserver variation among eight experienced histopathologists. The greatest disparity was noted in distinguishing indefinite for dysplasia from LGD and so these groups are often combined[18]. There was more agreement (88 per cent) when distinguishing high-grade dysplasia (HGD) and intramucosal carcinoma from all other grades. In practice, it is unnecessary and probably impossible to distinguish reliably between HGD and carcinoma *in situ*; the latter term has now been abandoned.

Cytological assessment of dysplasia

The main difficulty in relying on endoscopic biopsy for an accurate diagnosis is that areas of severe dysplasia or microinvasive cancer which exhibit a normal macroscopic appearance may be missed. Theoretically, sampling errors may be reduced by assessing brushings taken from the whole of the Barrett's epithelium[19]. There have been a number of studies examining the cytology of Barrett's oesophagus[19–22]. In a retrospective analysis of paired brushings and biopsies, Geisinger *et al.*[22] showed a 72 per cent concordance between the two methods, and that in eight of 64 cases brush cytology accurately identified the

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presence of dysplasia or cancer when the biopsy did not. Wang *et al.*[21] found that brush cytology was useful in identifying patients with and without dysplasia. However, they found it difficult to distinguish between LGD and HGD by cytology alone. Thus, the interobserver variation and subjectivity of cytological assessment mean that clinical decisions based on cytology alone are problematic and potentially dangerous. Results from biopsy and brushing methods, however, are likely to be complementary[19,22].

Objective assessment of dysplasia

Because of the subjectivity described above, attempts have been made to find a more objective means of diagnosing dysplasia. Most gastrointestinal cancers have aneuploid cell populations and Barrett's cancer is no exception. In one study, both aneuploidy and increased G2 fractions, determined by flow cytometry, were found to correlate closely with dysplasia, although one of 34 patients with non-dysplastic epithelium had both aneuploidy and increased G2 fractions[23]. In the more labour intensive technique of image cytometry, a similar correlation was found between aneuploidy, dysplasia and the subsequent development of adenocarcinoma[24]. In a prospective study, nine of 13 patients who had increased G2 fractions/tetraploid fractions or aneuploidy progressed to HGD over 34 months. None of 49 other patients without these abnormalities progressed[25].

Unfortunately, flow cytometric abnormalities are found in a subset of patients without dysplasia and four of six patients with HGD were found to have only diploid cell populations in a study by Fennerty *et al.*[26]. The presence of aneuploidy/increased G2 fractions/tetraploidy is not related to the degree of dysplasia but may be an independent high-risk marker in the younger patient[27]. This discordance means that the histological assessment of dysplasia is still the preferred routine method for assessing risk of malignant change. Further prospective studies are required to determine if patients who have flow cytometric abnormalities are at increased risk of developing dysplasia and cancer.

Evidence for a dysplasia – carcinoma sequence

In patients with Barrett's adenocarcinoma, dysplasia is commonly found in the surrounding areas of macroscopically 'normal' Barrett's epithelium. HGD is found adjacent to adenocarcinoma in 50–100 per cent of cases[28–32]; LGD is found less often[33]. Many studies have shown that there may be multifocal areas of dysplasia throughout the length of the Barrett's oesophagus[16,32,34]. Alternatively, the dysplasia may be present in zones which, in some cases, may be very extensive[18]. This field change is the likely reason for a few reports of second primary Barrett's adenocarcinomas arising after incomplete resection of the Barrett's epithelium[18,29,35]. Consequently, the aim of surgery should be to resect the tumour along with the whole of the Barrett's epithelium.

Notwithstanding the above, the most convincing evidence of a dysplasia – carcinoma sequence comes from prospective surveillance studies. In patients who eventually develop cancer, previous biopsies commonly show an increasing severity of dysplasia with time[13,31,36].

Incidence and natural history of dysplasia

In most series it is very difficult to estimate the prevalence of dysplasia in Barrett's oesophagus because of referral bias. Figures range from 2 to 24 per cent of HGD in tertiary surgical centres[23,26,28,36]. The prevalence of LGD is much higher, but apparent regression of this abnormality is much more common and it should not be considered as a high-risk marker[12,36–38].

The natural history of HGD is difficult to determine. First, because of sampling errors one cannot be sure when HGD is first present. Second, for the same reason, it is not possible to determine the precise point in time when the dysplastic cells become invasive. Some reports suggest that the change from HGD to cancer may occur over only a few weeks[31,36,37]. This may simply reflect a large sampling error since there are many other well documented cases of HGD remaining unchanged for up to 42 months[18,33,35,39–42]. Clearly, the sampling technique is the critical factor in determining the natural history of HGD. It is misleading to quote the time it takes to progress from non-dysplastic to dysplastic epithelium since it is not possible to determine when the Barrett's oesophagus first appeared. Again, owing to sampling error, it is not easy to be sure that HGD can regress. However, over a 3-year period, seven of 22 patients with HGD had no evidence of this feature on repeated biopsy, suggesting that it may have regressed[41]. There is a single case report of a patient with HGD in a short-segment Barrett's oesophagus who had complete regression of all metaplastic and dysplastic epithelium over a 6-year period[43]. It is not possible to conclude whether this was due to a proton pump inhibitor or the 190 biopsies that were taken.

Risk of cancer with high-grade dysplasia

Several studies (*Table 1*) have demonstrated that, when endoscopic biopsies show HGD, approximately 50 per cent of resected specimens contain evidence of invasive cancer. Of concern is that this has been reported as occurring in Barrett's oesophagus without any visually recognizable lesion at endoscopy[8,18,32,39,45]. It is primarily because of these data that surgery is recommended for HGD[29–31,33–35,45,46,48–51].

Nevertheless, it must be stressed that many of these reports are derived from small numbers of patients. Furthermore, in some reports it is not altogether surprising that many patients were eventually diagnosed as having Barrett's cancer. For example, Altorki *et al.*[46] found cancer in three of eight patients with Barrett's oesophagus (and in one with gastric heterotopia) with preoperative biopsies showing HGD. This is somewhat misleading since two patients had a cytological diagnosis of cancer, four had dysphagia, four had barium swallow abnormalities, two had polypoidal lesions, three had ulceration and one had a stricture. The results may simply reflect problems with sample error, even though biopsies were taken from all endoscopic abnormalities and every 1–2 cm throughout the length of the Barrett's epithelium. However, it was not stated whether the endoscopist had used jumbo biopsy forceps and four quadrant biopsies were not taken; both of these techniques are recommended to eliminate (some) sample error[12,18].

Similarly, Pera *et al*[35] reported nine of 18 patients who had unsuspected carcinoma in specimens resected for HGD. The endoscopic findings were abnormal in six of these nine cases[35]. The criticism by Levine *et al.*[42] that authors are not reporting the endoscopic findings is, unfortunately, still being ignored[48,49].

When patients with suspicious symptoms or endoscopic findings are excluded, the risk of missing an unsuspected carcinoma is low[41,47] and, using a more extensive biopsy protocol with jumbo forceps, this risk is further reduced[18,42]. The simultaneous presence of a Barrett's ulcer and HGD appears to be particularly suggestive of an unsuspected carcinoma[18,37,46,51]. In the largest study to date, no patient has died as a result of a missed carcinoma and no patient has been found to have an unsuspected carcinoma following surgery for HGD[42]. In another series of patients with HGD without cancer who had surveillance only, more patients died of unrelated causes than developed cancer[41]. This reflects the fact that many of these patients are elderly and have significant concurrent disease. Unfortunately, using an identical sampling method these encouraging results have not been repeated in other centres with two of 19 patients still having an unsuspected carcinoma in one recent report[52].

Endoluminal ultrasonography

Endoluminal ultrasonography is now widely used in the preoperative staging of oesophageal cancer. Its sensitivity and specificity are similar to those of computed tomography in detecting nodal metastases but ultrasonography may be superior in assessing depth of tumour penetration[53]. Consequently, there has been much recent interest in the potential of endoluminal ultrasonography in distinguishing between HGD and early invasive cancer.

Barrett's mucosa may appear significantly thicker than the normal squamous epithelium when measured by ultrasonography. In one series two patients with HGD had focal submucosal thickening detected ultrasonographically and the resected specimens both showed submucosal cancer[54]. In a much larger sample, however, the depth of invasion was assessed accurately in only six of nine intramucosal and 15 of 19 submucosal oesophageal carcinomas by preoperative endoluminal ultrasonography[55]. It could not differentiate between HGD and intraepithelial carcinoma. In two further series of 19 and nine patients with HGD/early carcinoma in Barrett's oesophagus ultrasonography did not accurately predict the presence or absence of invasion[52,56].

Treatment

Surgery

The decision to operate for HGD should be based on balancing the risk of missing unsuspected cancer against the risk of surgical morbidity and death. The operation should aim to remove all the Barrett's oesophagus[12,29] and so preoperative oesophagoscopy should be used to document accurately the level of the squamocolumnar junction. The 5-year survival rate of patients treated by surgical resection of HGD or stage I (submucosal) cancer is between 80 and 100 per cent[8,29,35,46]. However, the morbidity associated with surgery is significant, even following resection of dysplastic epithelium[8,45]. In specialist centres the mortality rate is lower, averaging 4 per cent[48], but generally rates vary between 0 and 25 per cent[8,18,35,45]. Continued surveillance, therefore, may be more appropriate in some cases, especially in non-specialist centres[18,36,42]. This is still a difficult issue because there has been no randomized trial of surgery *versus* surveillance for patients with HGD in Barrett's oesophagus. It is unlikely that this will ever be done because, even in the largest centres, the number of eligible patients is very small.

Antireflux surgery is not advised for patients with confirmed HGD in case unrecognized foci of micro-invasion are present. The role of antireflux surgery in the prevention of neoplastic progression has not yet been subjected to a randomized controlled trial. Skinner and colleagues[30] have advocated this type of surgery regardless of symptoms, based on data from just three patients who were documented as having severe reflux and progression of dysplasia, and one patient who had apparent regression of LGD after a successful antireflux repair. The numbers are very small and no meaningful conclusion can be

Table 1 Reported rates of adenocarcinoma in oesophagectomy specimens from patients whose endoscopic biopsies showed only high-grade dysplasia

Reference	Year	No. of patients with preoperative diagnosis of HGD	No. of patients with cancer in resected specimen	Missed cancers (%)
Reid *et al.*[18]	1988	4	0	0
DeMeester *et al.*[28]	1990	2	1	50
Streitz *et al.*[29]	1993	9	2	22
Skinner *et al.*[30]	1983	3	2	67
McArdle *et al.*[32]	1992	3	2	67
Hamilton and Smith[33]	1987	3	2	67
Pera *et al.*[35]	1992	18	9	50
Lee[44]	1985	4	3	75
Schnell *et al.*[41]	1989	43	21	49
Levine *et al.*[42]	1993	7	0	0
Rice *et al.*[45]	1993	16	6	38
Altorki *et al.*[46]	1991	8	3	38
Wright *et al.*[47]	1994	15	7	47
Edwards *et al.*[48]	1996	11	8	73
Heitmiller *et al.*[49]	1996	30	13	43

HGD, high-grade dysplasia

reached from what was a very selected group of patients. An important finding of the study by Skinner was that complete regression of the Barrett's epithelium is rare and apparent partial regression is simply due to the surgical relocation of the squamocolumnar junction. Furthermore, columnar epithelium was found beneath the regenerating squamous islands after surgery[30]. Thus even extensive squamous islands (which also occur after treatment with proton pump inhibitors[57]) cannot be regarded as a feature of partial regression. It is unknown whether the Barrett's epithelium under squamous islands has the same malignant potential as the untreated exposed Barrett's epithelium, but there is a report of adenocarcinoma arising in a Barrett's oesophagus which had developed extensive squamous islands following antireflux surgery and proton pump inhibition[58].

There are many reports of Barrett's cancer following successful antireflux surgery[13,29,34,50,59–61]. Rosenberg *et al.*[34] reported four cancers in nine operated patients and Streitz and colleagues[29] reported five also in nine operated patients. It is, however, difficult to avoid selection bias in the surgical literature and the proportion of cancers developing after apparently successful antireflux surgery in these two reports does appear to be extraordinarily high. A prospective randomized trial seems warranted to define the role of antireflux surgery in the prevention of neoplastic progression. On the basis of current evidence, the main aim of antireflux surgery in Barrett's oesophagus should be to control symptoms and not to induce regression or reduce the risk of malignancy.

Thoracoscopically assisted oesophagectomy has the theoretical advantages of potentially reducing morbidity and mortality rates[62]; this approach seems highly desirable for HGD when lymph node clearance is unnecessary. Unfortunately, the advantages of the technique have not been realized in early reports and it cannot be recommended until more experience has been obtained[63,64].

Ablation therapy

It is not surprising, in the current climate of minimally invasive surgery, that there are now alternative therapeutic options which ostensibly do not carry the risk of major surgery. By creating ulceration of the lower oesophagus and allowing healing in an acid environment, Gillen *et al.*[65] showed that Barrett's epithelium could be reproduced. In the absence of acid, however, healing occurred with squamous epithelium. This prompted Brandt *et al.*[66] to attempt laser ablation of a short-segment Barrett's oesophagus after a successful antireflux operation, with the hypothesis that healing would be by squamous epithelization. Despite the addition of a proton pump inhibitor, the initial squamous regeneration was eventually replaced by a recurrence of columnar epithelium. This disappointing result may have resulted from failure to destroy completely the epithelium, since columnar epithelium is often seen underlying squamous regeneration[67–69].

In non-dysplastic Barrett's oesophagus, in one series complete squamous re-epithelialization occurred in three of 11 patients treated with proton pump inhibitors and multipolar electrocoagulation[68], and in all ten patients treated with a neodymium yttrium–aluminium–garnet (NdYAG) laser after antireflux surgery[70]. NdYAG laser therapy with proton pump inhibition has been used in a single case of HGD and early focal adenocarcinoma; it produced a temporary resolution[69]. Barrett's cancer has been reported following only partial regression and so it would seem that complete eradication of all of the metaplastic epithelium is required to eliminate this risk[58].

Endoscopic mucosal resection of early oesophageal cancer is claimed to give a 95–100 per cent 5-year survival rate, a 3–7 per cent local recurrence rate and a very low complication rate[71]. Further studies are required to confirm these findings. Although patients with HGD may be a group which is ideally suited to ablation therapy, the potential benefits of such treatment need to be considered in relation to its complications. Numbers are few, but retrosternal discomfort, haemorrhage, odynophagia, perforation and stricture formation have all been reported[67,68,71]. The problem of late recurrence requires longer prospective trials.

Photodynamic therapy

Photodynamic therapy involves tissue destruction induced by laser light following the systemic administration of a photosensitizing agent. Recent refinements mean that the initial poor results are being bettered. Ideally the photosensitizer should be taken up selectively by neoplastic tissue and have a short half-life; one popular preparation is haematoporphyrin derivative. Problems with cutaneous sensitivity last up to 6 weeks[72] and uptake in non-neoplastic epithelial cells may result in stricture after treatment[73]. Nevertheless, it has been used to induce complete and partial regression of non-dysplastic Barrett's oesophagus[74].

Using 5-aminolaevulinic acid (5-ALA) reduces the side-effects of photodynamic therapy. It is a prodrug that is converted into the active compound, protoporphyrin IX, and cutaneous photosensitivity is limited to 1 or 2 days. The agent is taken up selectively in neoplastic mucosa rather than connective tissue and, theoretically, should result in fewer strictures. It also has the advantage of oral administration[72].

The dosage of the photosensitizer and total amount of light energy given are critical. Low-dose regimens may be the reason for only superficial mucosal necrosis. Different regimens are required at different tumour sites. For example, higher doses are required for colonic than for oesophageal tumours[72]. However, higher doses may cause more extensive damage, resulting in pain, ulceration and stricture formation[73].

Unfortunately there are several variables which confound comparison of photodynamic therapy in different reports. It is likely that many total failures are attributable to a drift in the wavelength of the light[73,75,76]. A variety of wavelengths has been used, ranging from 630 to 635 nm[72–74,77]. Using 5-ALA 60 mg/kg and a laser light dosage of 150 J/cm^2 at a wavelength of 635 nm, an 80 per cent complete response rate was found in five patients with HGD in Barrett's oesophagus[77]. This is in contrast to only superficial necrosis (at most) after 5-ALA 30 mg/kg and a laser dosage of only 75 J/cm^2 at 632·8 nm wavelength[72]. Another study, examining gastric adenocarcinoma and oesophageal squamous carcinoma, described a complete response in 51 per cent of patients at 4 months after photodynamic therapy using haematoporphyrin derivative and laser light of 632 nm at 220 J/cm^2. Treatment failure was commoner in aneuploid tumours[78].

Only tumours at an early stage allow a good response to photodynamic therapy and in Barrett's adenocarcinoma endoluminal ultrasonography helps to confirm this[73,78]. Complete destruction of HGD has been reported in all six patients using 5-ALA at 60 mg/kg and laser light of 630 nm at 90–150 J/cm^2 (Ref. 79). Such treatment, therefore, appears to have its greatest potential benefit in treating patients with HGD and early Barrett's adenocarcinoma, especially those who are high-risk candidates for operation.

Conclusion

A histological diagnosis of HGD requires confirmation from a second experienced pathologist. Young fit patients with HGD in Barrett's oesophagus should still be offered operation for fear of missing early cancer. In less fit patients, surgery may be reserved until endoscopic surveillance detects evidence of invasion. There is no evidence supporting a role for antisecretory therapy or antireflux surgery in the treatment or prevention of dysplasia in Barrett's oesophagus. New advances in endoscopy mean that some high-risk patients can now be offered potentially curative non-invasive therapy as an alternative to continued surveillance. A selective approach to the management of HGD on an individual patient basis should be adopted.

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SURGERY TODAY
The Japanese Journal of Surgery

Digest

Dr Keizo Sugimachi, Editor-in-Chief of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the October, November and December 1996 issues of his journal for this quarter's digest. A digest of *BJS* for the same period written by Mr Colin Johnson, European Editor, appears in the Japanese journal.

Colorectal carcinoma

The presence of human β-chorionic gonadotropin (hCG) was studied immunohistochemically in 123 patients with primary colorectal carcinoma using the avidin–biotin–peroxidase complex method[1]. Positive staining for hCG was recognized in 45 tumours (36·6 per cent) and a statistical difference was observed between the hCG-positive and hCG-negative groups with regard to the frequency of blood vessel invasion in the primary tumour ($P < 0{\cdot}01$). The prognosis for patients with hCG-positive carcinoma was significantly worse than that for those with hCG-negative tumours ($P < 0{\cdot}05$). Multivariate analysis using the Cox hazards model demonstrated positive or negative staining of hCG to be an independent prognostic factor. These findings show that, in addition to various other prognostic factors. hCG staining status may also help in determining the prognosis of patients with primary colorectal carcinoma.

The results of laparoscopy-assisted colectomy in 20 patients with invasive carcinoma of the colon were analysed[2] The site of the lesion was the right colon in five patients, the transverse colon in one, the left colon in 13 and the rectosigmoid in one. In two patients, the laparoscopic procedure had to be converted to open laparotomy. Limited lymph node dissection (R_{1+}, R_2) was carried out in ten patients, and extensive node dissection (R_3) in nine. The histological depth of invasion in the 18 patients who underwent laparoscopy-assisted colectomy was to the submucosa in nine, to the muscularis propria in two, and to the extramuscular layer in seven. Three patients developed postoperative complications, one of whom underwent reoperation because of perforation of the colon.

The postoperative course of the patients who underwent laparoscopic surgery was compared with that of a retrospectively selected control group of patients who had undergone open laparotomy. Postoperative recovery of patients who had laparoscopic surgery was significantly faster than that of those who had the open procedure. Thus, the authors consider that laparoscopy-assisted colectomy with lymph node dissection is technically feasible provided the patients are properly selected. This procedure may be indicated not only for colonic carcinoma in the early stage, but also for cancer with invasion of the muscularis propria or extramuscular layer.

Breast carcinoma

The clinical characteristics of five male patients with breast carcinoma and a family history of breast cancer were described[3]. Four of these patients suffered from multiple primary cancers: gastric and prostate cancer in one, gastric cancer in one and asynchronous bilateral breast cancers in two. The average age of these patients at diagnosis was no lower than that of men with breast carcinoma and no such family history. The aggregation of cancer in these families had three prominent characteristics: (1) the families included women with early-onset breast cancer, which had occurred at the ages of 38, 38 and 35 years, and/or early-onset uterine cancer, which had occurred at the age of 35 years; (2) the incidence of multiple primary cancers was significantly higher in the siblings of male patients with breast carcinoma and a family history of breast cancer than in those without; (3) there were many cancers in hormone-related organs in two families.

Inactivation of the 'deleted in colonic cancer' (*DCC*) gene on chromosome 18 is known to be associated with the tumorigenesis and metastasis of colorectal cancer[4]. Wakita *et al.* investigated the expression of *DCC* and the *C-erbB-2* product in surgical specimens from 45 patients with breast cancer by immunohistochemical staining, and found the expression of *DCC* to be decreased in 23 tumours. In 8 years of follow-up, 11 of 22 patients with *DCC*-positive tumours, and 17 of 23 with *DCC*-negative tumours, developed recurrence. The stratified analysis, according to the status of axillary lymph node metastasis, showed the same tendency. Overexpression of *erbB-2* was detected in 13 of the 45 breast cancer specimens, but there were no differences in the relapse rate between patients with *erbB-2*-positive and *erbB-2*-negative tumours. Although the individual alteration of *DCC* or *erbB-2* did not demonstrate independent prognostic significance for the prediction of recurrence, patients with tumours that were both *DCC* negative and *erbB-2* positive showed reduced relapse-free survival ($P < 0{\cdot}05$). These findings suggest that a decrease in *DCC* expression and *erbB-2* overexpression may influence the progression of breast carcinoma.

Cardiac surgery

Wang *et al.*[5] studied the effect of nicorandil on the haemodynamic, biochemical and ultrastructural changes in rabbit hearts rendered cardioplegic with a single injection of Bretschneider's HTK solution over 30 or 60 min at 37 or 15°C, followed by reperfusion at 37°C for 60 min. Particular attention was focused on the dose–response relationship, temperature sensitivity and ischaemic tolerance. Isolated hearts were prepared for modified Langendorff circulation using modified Krebs–Henseleit bicarbonate solution bubbled with a 95 per cent oxygen and 5 per cent carbon dioxide gas mixture, to which nicorandil (0, 0·1, 1 and 5 mmol/l) was added. The optimal concentration of nicorandil was 1 mmol/l, which increased the recovery of left ventricular (LV) function, affecting coronary flow and myocardial cyclic adenosine 5′-monophosphate levels, but not the myocardial concentration of adenine nucleotide compounds or total calcium. These effects were abolished by the addition of glibenclamide, but they were not diminished by a high potassium concentration of 20 mmol/l. The addition of nicorandil 1 mmol/l at 15°C did not improve the recovery of LV function. These results suggested that nicorandil prevents LV functional depression after 30 min, and possibly 60 min of cardioplegia at 37°C, and that this effect is not disturbed by a high potassium concentration of up to 20 mmol/l. However, nicorandil is temperature sensitive whereby it loses its efficacy at 15°C.

Six patients underwent open heart surgery for mitral valve disease following percutaneous transvenous mitral commissurotomy (PTMC) because of recurrent mitral stenosis in four, moderate mitral regurgitation in one, and acute severe mitral regurgitation in one[6]. These six patients were the only such observed cases of a total of 86 who presented with PTMC between October 1989 and May 1995. The mean(s.d.) duration of subjective symptoms related to heart failure was 24·1(11·6) (range 3–30) years. Four of the six patients had undergone a previous surgical commissurotomy (closed mitral commissurotomy in two and open mitral commissurotomy in two) 24–30 (mean 28) years earlier. Intraoperative findings in the four patients with residual mitral stenosis included severe thickening, calcification on anterior and posterior leaflets, and bilateral commissures. Five patients were noted to have shortening and adhesion in the mitral subvalvular apparatus. Two patients with moderate to severe tears on the anterior leaflets, and a further two with tears on the posterior leaflet, were also noticed; however, these leaflets were not severely thickened. It was possible to split and repair the fused commissure in one patient, but the other five required mitral valve replacement due to severe subvalvular lesions. Therefore, if a patient has bilateral commissural calcification or less thickened leaflets with severe subvalvular thickening and fusion with a small mitral valve area measuring less than 0·8 cm^2 and a mitral stenosis score of more than 8, open commissurotomy is considered to provide good long-term clinical results. The decision to perform either PTMC or open mitral commissurotomy should be based on meticulous echo Doppler ultrasonographic findings and haemodynamic evaluation of the mitral valve.

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For debate

CONSORT, randomized trials and the surgical scientific community

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The recent engagement of Horton[1], who accused surgeons of not performing enough randomized trials, with Bell and others[2] has left an insulted surgical community. But others have criticized clinical surgical research too[3,4]. Ignore or improve? While it is true that surgical research can be performed outside the framework of trials and that there are some practical issues to be solved in trials[5,6], it is also true that high-quality surgical trials have been done in the past and can still be done today. It has been suggested that funding is more difficult to obtain for surgical than for medical trials but is this sufficient to explain the scarcity of good surgical trials? It surely is not an argument to explain the lack of quality in some of them.

Solomon *et al.*[7] have studied surgical trials and found that those appearing in surgical journals were of poor quality; only one-third had a surgeon as principal author. Few trials assessed the value of operations. When we review surgical trials, can we ignore the observation that their methods sections are frequently tiny, lacking power calculations and adequate definitions of outcome?

The CONSORT (Consolidated Standards of Reporting Trials) statement is a new development concerning the quality of randomized trials[8] which has been encouraged by three leading (medical) journals[9–11] whose trial reporting is supposed to be better than that of surgical journals. CONSORT guidelines (*Appendix 1*) were adopted by these journals from January 1997 and, if strictly adhered to, will prevent the publication of surgical trials such as (most of) those described by Solomon *et al.*[7]. CONSORT may lead to a new publication standard for randomized trials; all manuscripts to be considered for publication by CONSORT journals will have to include a 21-item checklist, mainly focusing on the methods section, and a flow chart providing information on participant flow and follow-up.

Even though blinding (masking) was carried out in the recent trial of techniques of cholecystectomy which was reported in *Lancet* by Majeed *et al.*[12], can we really expect all trials to be performed in such a fashion? Such a trial method may not be so difficult in a single institution, but multi-institutional trials might become impossible as they depend on effort from personnel only indirectly involved or controlled. Withdrawing patients from study after randomization is not rare, but in surgical trials it appears to be quite common. Does this reflect lack of quality? In some cases, such as Majeed's[12] and the Dutch gastric cancer trial[13], withdrawal could not be prevented because certain inclusion criteria could sometimes only be determined during operation

What do editors of surgical journals think of CONSORT? Surely it should be seen as a change for the better? Is it too simple just to say we too will implement CONSORT? Should we, perhaps, adapt CONSORT, or should we apply it with some lenience to surgical trials?

In any case, CONSORT is a serious attempt to improve quality and ease of interpreting results. In view of this we can, perhaps, ask surgeons undertaking trials to determine appropriate and well defined endpoints, and to perform realistic power calculations. Still, the design and execution of large trials is not an easy task for most surgeons in clinical practice, although they are the ones called upon to implement change in the light of trial results. Full-time assistance for data management and the help of epidemiologists may be indispensable. Perhaps surgeon–epidemiologist should be more than just a theoretical notion.

The surgical scientific community should take CONSORT seriously. Surgical trials are necessary; they should not be allowed to become extinct or to be of poorer quality than other trials. Surgical researchers will want to know the opinions of editors of surgical journals and the likely future policies of these journals which embody our scientific efforts.

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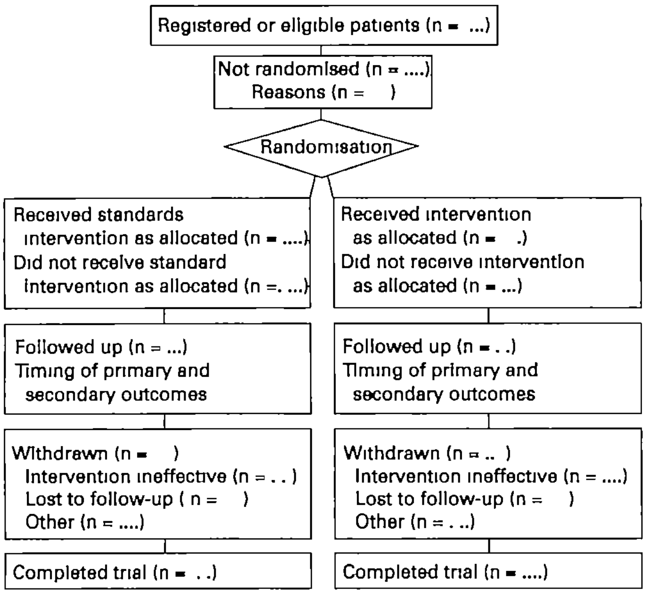
Appendix


Registered or eligible patients (n = ...)
Not randomised (n = ...)
Reasons (n =)
Randomisation
Received standards intervention as allocated (n = ...)
Did not receive standard intervention as allocated (n =. ...)
Received intervention as allocated (n = .)
Did not receive intervention as allocated (n = ...)
Followed up (n = ...)
Timing of primary and secondary outcomes
Followed up (n = . .)
Timing of primary and secondary outcomes
Withdrawn (n =)
Intervention ineffective (n = . .)
Lost to follow-up (n =)
Other (n = ...)
Withdrawn (n = ..)
Intervention ineffective (n = ...)
Lost to follow-up (n =)
Other (n = . ..)
Completed trial (n = . .)
Completed trial (n = ...)

Appendix 1a Flow chart describing progress of patients through randomized trial. Reproduced with permission from *JAMA* 1996; 276: 638. Copyright 1996, American Medical Association

Appendix 1b Items that should be included in reports of randomized trials

Heading	Subheading	Descriptor
Title		Identify the study as a randomized trial
Abstract		Use a structured format
Introduction		State prospectively defined hypothesis, clinical objectives, and planned subgroup or covariate analyses
Methods	Protocol	Describe
		Planned study population, together with inclusion or exclusion criteria
		Planned interventions and their timing
		Primary and secondary outcome measure(s) and the minimum important difference(s), and indicate how the target sample size was projected
		Rationale and methods for statistical analyses, detailing main comparative analyses and whether they were completed on an intention to treat basis
		Prospectively defined stopping rules (if warranted)
	Assignment	Describe
		Unit of randomization (for example, individual, cluster, geographical)
		Method used to generate the allocation schedule
		Method of allocation concealment and timing of assignment
		Method to separate the generator from the executor of assignment
	Masking (blinding)	Describe
		Mechanism (for example, capsules, tablets)
		Similarity of treatment characteristics (for example, appearance, taste)
		Allocation schedule control (location of code during trial and when broken)
		Evidence for successful blinding among participants, person doing intervention, outcome assessors and data analysts
Results	Participant flow and follow-up	Provide a trial profile (a) summarizing participant flow, numbers and timing of randomization assignment, interventions, and measurements for each randomized group
	Analysis	State estimated effect of intervention on primary and secondary outcome measures, including a point estimate and measure of precision (confidence interval)
		State results in absolute numbers when feasible (for example, 10 of 20 not 50 per cent)
		Present summary data and appropriate descriptive and interferential statistics in sufficient detail to permit alternative analyses and replication
		Describe prognostic variables by treatment group and any attempt to adjust for them
		Describe protocol deviations from the study as planned, together with the reasons
Discussion		State specific interpretation of study findings, including sources of bias and imprecision (internal validity) and discussion of external validity, including appropriate quantitative measures when possible
		State general interpretation of the data in light of the totality of the available evidence

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Candida antigen titre dilution and death after injury

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Background *Candida* infections affect outcome after injury. *Candida* antigen titres were used to detect these infections early. This study was undertaken to correlate *Candida* antigen titre dilution with conventional injury scoring and outcome after severe injury.

Methods *Candida* antigen titres were determined by agglutination when clinically apparent source(s) of *Candida* were noted, when *Candida* was grown in culture of body fluids, or when unexplained clinical deterioration occurred. The findings were compared with the Injury Severity Score (ISS).

Results Seventy-five seriously injured adults (median ISS 25 (range 18–50)) developed raised *Candida* antigen titres. Multivariate analysis showed that age and *Candida* antigen titre correlated significantly with mortality, but not with each other. Culture evidence of *Candida*, or lack thereof, did not correlate with *Candida* antigen titre or mortality. Sixteen of 75 patients died, 14 from bacterial sepsis and none from *Candida* infection.

Conclusion In seriously injured adults, the mortality rate is related to raised *Candida* antigen titres. The association between *Candida* antigen titre and mortality, although real, remains unexplained.

Physicians have long been aware that *Candida* infections occur in severely ill patients requiring intensive care[1–4]. Despite this attention, considerable debate continues regarding some fundamental aspects of *Candida* infection.

There is little disagreement that documented candidaemia is associated with a high mortality rate in surgical patients[5–7] and that advanced invasion warrants systemic antifungal therapy. Great disagreement exists, however, as to what constitutes early, yet significant, *Candida* invasion[1,8–13]. The clinical implications of this disagreement are considerable. Presently, clinical impressions and practical experience determine the use of antifungal therapy. Now, the availability of antifungal therapy thought to be less toxic but as efficacious as previous therapies[14,15] has added to the antifungal armamentarium, but not to the logic with which such therapy is applied.

To guide antifungal therapy, reliable non-invasive methods for the accurate and early detection of *Candida* invasion have been sought. *Candida* antibody titres correlate poorly with the clinical diagnosis of candidiasis and outcome[8,13,16]. Fungal cell wall metabolites[16,17] and the expression of fungal cytoplasmic antigens[18] correlate poorly with known *Candida* invasion. In this study a latex agglutination test, which has recently become available commercially for the detection of an uncharacterized *Candida* cell wall antigen, was used. This test can detect systemic candidiasis in patients suffering from underlying malignancy and receiving chemotherapy[9–12,19–23] with a generally high, but variable, sensitivity and specificity. The wide range of sensitivity and specificity reported in the literature[8–12,16,21–25] has prevented acceptance of this assay by clinicians seeking a definitive serological marker for *Candida*. The determination of sensitivity and specificity, however, requires that test results be evaluated relative to the standard for *Candida* invasion: positive blood cultures. In the absence of documented candidal invasion by a traditional marker, a raised *Candida* antigen titre is assigned a false-positive label rather than regarded as a marker of occult *Candida* invasion.

The authors sought to determine the implications of increased *Candida* antigen titres in critically ill victims of severe trauma. These patients are particularly at risk of fungal invasion. The hypothesis in undertaking this study was that *Candida* antigen titre dilution would correlate with traditional prognostic scoring systems (Injury Severity Score (ISS) and Trauma and Injury Severity Score (TRISS)) and ultimately with outcome.

Patients and methods

All patients older than 18 years who had sustained blunt or penetrating trauma, with an ISS greater than or equal to 18, who were not pregnant, not receiving antifungal therapy, and survived the first 72 h of admission had *Candida* antigen titres determined (Cand-Tec, Ramco Laboratories, Houston, Texas, USA) when clinically apparent source(s) of *Candida* were noted, when *Candida* was grown in culture of body fluids, or when unexplained clinical deterioration occurred. A total of 161 consecutive patients (representing 8 per cent of total trauma admissions over this time period) meeting these criteria were tested. Seventy-five patients had raised titres and were followed prospectively for survival. These 75 patients are the population of this study. All patients were cared for in a university-affiliated level I trauma centre.

Control sera were included in each assay. *Candida* antigen titres were defined as 'raised' if they were equal to or greater than 1·4 *Candida* antigen titres were unknown to the treating physicians and so did not influence the initiation of antifungal therapy. Antifungal therapy was empirical or administered because of clinically apparent or culture-documented sources of *Candida*. Patients inadvertently receiving antifungal therapy without documented candidal infection were considered protocol violations and were excluded. The first 25 patients enrolled in the study received a short course of low-dose amphotericin B[26]; the remaining patients received fluconazole (400 mg loading dose followed by 200 mg per day for a further 6 days). With the initiation of systemic antifungal therapy, central venous catheters were cultured and replaced, or changed to a new site.

Data collected were age, sex and ISS, determined at discharge or autopsy[27]. All clinical and empirical diagnoses were recorded. *Candida* antigen titres and culture results were noted, as well as the type and severity of documented infections, the number and type of antibiotics used, the duration of antibiotic therapy, and the type and duration of antifungal therapy. Operative interventions were also noted. Predicted survival for each patient

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was approximated using TRISS methodology[28]. Patients were stratified by their highest *Candida* antigen titre during hospitalization. Mortality rates were determined for each *Candida* antigen titre dilution and were correlated with patient demographic information, *Candida* antigen titre, ISS and predicted survival rates Data were analysed with Kwikstat 2.00 (TexaSoft/Mission Technologies, Cedar Hill, Texas, USA) on an IBM-compatible personal computer. Significance was assigned with 95 per cent confidence (i.e. $P<0{\cdot}05$) No assistance from Ramco Laboratories was sought or offered in undertaking this study.

Results

Seventy-five injured adults, 59 men and 16 women of mean(s.d.) age 41(18·2) years, developed raised *Candida* antigen titres during hospitalization. Sixty-seven patients (89 per cent) had blunt trauma, six (8 per cent) had gunshot injuries and two (3 per cent) were burned. Median ISS for patients with raised titres was 25 (range 18–50). At the time of documented increased *Candida* antigen titres, all patients were receiving aggressive support, including antibiotics, and 71 (95 per cent) had at least one documented bacterial infection, often polymicrobial (80 per cent). No patient was receiving antifungal therapy when titre status was determined.

TRISS methodology predicted a mortality rate of 13 per cent, whereas the actual mortality rate was significantly higher at 21 per cent (confidence interval 0·69–4·57; $P=0{\cdot}002$, Fisher's exact test). None of the patients who died demonstrated culture evidence of *Candida*, candidaemia, or visceral candidiasis. Sex, mechanism of injury, frequency of documented bacterial infections, ISS and predicted survival (TRISS methodology) did not differ between patients who lived or died (*Table 1*), although survivors were younger ($t=3{\cdot}21$, $P<0{\cdot}01$, Student's t test).

Table 1 Comparison between injured adults with raised *Candida* antigen titres who lived or died

	Survivors	Deaths
No. of patients	59	16
Mean(s.d.) age (years)	39(16·1)	54(16·0)†
Sex ratio (M:F)	46:13	13:3
Blunt trauma (%)	90	88
Infection (%)*	93	100
Median (range) ISS	25 (18–50)	25 (25–50)
Median (range) TRISS	0·85 (0·22–0·99)	0·98 (0·48–0·99)

*Documented infection at the time of raised *Candida* antigen titre. ISS, Injury Severity Score; TRISS, Trauma and Injury Severity Score. †$P<0{\cdot}01$ *versus* survivors (Student's t test)

Twenty-nine patients (39 per cent) developed *Candida* antigen titres of 1:4, 22 (29 per cent) developed titres of 1:8, 14 (19 per cent) developed titres of 1:16, nine (12 per cent) developed titres of 1:32 and one (1 per cent) developed a titre of 1:64. Age, sex, mechanism of injury, frequency of concomitant bacterial infection, ISS and predicted survival did not vary significantly among injured patients with different *Candida* antigen titre dilutions (*Table 2*). Survivors and non-survivors were similar with regard to sex, mechanism of injury, frequency of documented bacterial infection, ISS and predicted survival at each titre of *Candida* antigen (data not shown). The mortality rate increased as *Candida* antigen titre increased (*Table 3*). By linear regression analysis, mortality was significantly related to *Candida* antigen titre (Pearson's $\rho=0{\cdot}47$, $R^2=0{\cdot}22$, $t=4{\cdot}60$, $P=0{\cdot}001$). Mortality was also related to age by regression analysis (Pearson's $\rho=0{\cdot}30$, $R^2=0{\cdot}09$, $t=2{\cdot}69$, $P=0{\cdot}009$). By linear regression analysis, however, titre and age were not related significantly (Pearson's $\rho=0{\cdot}14$, $R^2=0{\cdot}02$, $t=1{\cdot}21$, $P=0{\cdot}231$).

Multivariate regression analysis using seven independent variables (titre, age, sex, mechanism of injury, frequency of concomitant bacterial infection, ISS and predicted survival) documented a modest correlation of all variables with mortality ($R^2=0{\cdot}31$). For the regression analysis of all variables combined, analysis of variance documented a significant regression relation ($F=4{\cdot}35$, $P=0{\cdot}0005$). In this multivariate regression analysis, specific correlation existed only between mortality and titre ($t=4{\cdot}09$, $P=0{\cdot}0001$), and mortality and patient age ($t=2{\cdot}53$, $P=0{\cdot}014$). Using only these significant variables (*Candida* antigen titre dilution and patient age) multivariate regression analysis was repeated, and documented again that both titre ($t=4{\cdot}36$, $P=0{\cdot}0001$) and age ($t=2{\cdot}36$, $P=0{\cdot}021$) were significantly related to mortality ($R^2=0{\cdot}28$). Analysis of variance using these two variables only documented a significant regression relation ($F=14{\cdot}00$, $P=0{\cdot}00005$).

Clinical or culture evidence of *Candida* did not correlate with survival. *Candida* growth occurred in only

Table 3 Mortality as a function of *Candida* antigen titre dilution

Titre dilution	No. of deaths
1:4	1 of 29
1:8	6 of 22
1:16	4 of 14
1:32	4 of 9
1:64	1 of 1

Table 2 Comparison of injured adults with different *Candida* antigen titre dilutions

	Titre dilution				
	1:4 ($n=29$)	1:8 ($n=22$)	1:16 ($n=14$)	1:32 ($n=9$)	1:64 ($n=1$)
Mean(s.d.) age (years)	41(18·8)	42(16·4)	44(17·6)	49(22·8)	45
Blunt trauma (%)	93	91	79	88	100
Infection (%)*	86	100	100	100	100
Median (range) ISS	26 (18–50)	24 (18–48)	25 (19–43)	25 (18–50)	25
Median (range) TRISS	0·93 (0·13–0·99)	0·93 (0·30–0·99)	0·92 (0·21–0·99)	0·93 (0·22–0·99)	0·99

*Documented infection at the time of raised *Candida* antigen titre. ISS, Injury Severity Score; TRISS, Trauma and Injury Severity Score

18 cultures from 15 (20 per cent) of the 75 patients. Culture evidence of *Candida* was not related to titre dilution: ten of the 15 patients with culture evidence of *Candida* had a titre of 1:4 or 1:8. *Candida* grew most commonly in cultures of urine (five) and sputum (five). Cultures of central venous catheters from three patients yielded *Candida*. *Candida* also grew in single cases, in cultures of bile, peritoneal fluid, pleural fluid and an abdominal wound. No patients had *Candida* growth in blood cultures. *Candida* grew in cultures of body fluids from only four of 16 patients who subsequently died: in urine from two, sputum from one and pleural fluid from one. In none of these four patients did the *Candida* in culture appear to contribute to the patient's death.

Twenty-two (29 per cent) of the 75 patients did not receive systemic antifungal therapy. Fourteen of the 22 untreated patients had titres of 1:4. Of the 46 patients with titres greater than 1:4, 38 received systemic antifungal therapy. Twenty-two patients had a raised titre more than once during hospitalization and thereby received more than one course of antifungal therapy. Four of these patients ultimately died, two with highest titres of 1:8 and two with highest titres of 1:16.

Discussion

Candida infection can be difficult to differentiate from *Candida* colonization[1]. This difficulty is not trivial because, although *Candida* colonization is probably harmless, *Candida* invasion carries a high mortality rate in surgical patients[5-7,26]. Recognition of occult candidal invasion by a serological marker would allow early initiation of antifungal therapy and, presumably, best chance of cure. This study documents the relationship between an increase in *Candida* antigen titre and death in severely injured adults stratified by conventional scoring measures.

The 75 adults in this study were generally severely injured men who had suffered blunt trauma. The mortality rate of these injured adults with raised titres was considerably higher than that predicted by TRISS methodology, documenting the utility of *Candida* antigen titre in predicting outcome after severe injury. The use of TRISS in this report warrants comment. TRISS is frequently used to describe the severity of injury by predicting survival after injury. TRISS can be used appropriately to predict mortality for an injured adult or mortality within a population of injured adults. In this study, however, analysis is being made of a subgroup of a population, specifically a group of patients who had to survive for at least 3 days before titres were drawn. Comparisons made in this study of actual mortality with mortality predicted by TRISS must be viewed with caution, however, because the application of TRISS to subgroups compromises its validity. None the less, TRISS should have overpredicted mortality because a number of patients were excluded by their death. In other words, in this group of survivors, survival rate would have been expected to be better than that predicted by TRISS. In fact, TRISS underpredicted mortality, supporting the utility of the *Candida* antigen titre in predicting mortality in severely injured adults.

In this report, survivors and non-survivors were very similar with respect to conventional injury scoring. Only *Candida* antigen titre and age had a significant correlation with mortality, although they had no relationship to each other. *Candida* antigen titre had a stronger correlation with mortality than did age. That age had an independent effect on mortality in severely injured adults with raised *Candida* antigen titres is consistent with clinical experience demonstrating that older patients are less able to survive serious injury than their younger counterparts.

Mortality correlated with the level of titre increase, not the frequency with which patients developed raised titres. Nearly one-third of the patients developed more than one raised titre during hospitalization and their mortality rate (four of 22) was near that of the patients as a whole (21 per cent). Having more than one raised titre was not an ominous sign as mortality seems to correlate more closely with titre dilution than with the frequency of raised titres.

Candida growth in culture did not correlate with titre increase or mortality rate. Only a minority of patients in this report actually had culture proven sources of *Candida*. *Candida* in culture may represent colonization and does not always represent true invasion[24,29]; therefore, it is not surprising that titre dilution and culture results did not correlate.

Why *Candida* antigen is an independent predictor of outcome after serious injury remains a point of speculation. The logical interpretation is that injured adults with raised *Candida* antigen titres succumb to candidal invasion. This interpretation is thwarted by the observation that no death in this study was attributable to overt *Candida* invasion or infection. Conversely, patients who died did so because of bacterial (generally polybacterial) sepsis. The best interpretation of this observation is that occult candidal invasion, as denoted by the raised *Candida* antigen titres, seems to be associated with an increased lethality of bacterial infection, to a degree that is proportional to *Candida* antigen titre dilution.

How does occult candidal invasion translate into polybacterial sepsis? The authors believe that raised titres are a marker of global immune compromise and thus predispose critically ill patients to bacterial invasion and subsequent bacterial death. Previous studies undertaken in the authors' laboratory have documented neutrophil anticandidal dysfunction in patients with raised titres[30,31]. This anticandidal dysfunction was reversed when polymorphonuclear neutrophils (PMNs) were preincubated with proinflammatory cytokines. The authors speculated that these cytokines were released by lymphocytes, and further investigation revealed that lymphocytes from titre-positive patients were defective in their ability to release PMN-activating factors[31]. Documented global immune dysfunction, as predicted by titre positivity, renders patients susceptible to bacterial infection. The authors' laboratory is currently attempting to document this impaired response to bacterial stimuli by PMNs and lymphocytes in patients with raised titres.

Finally, how can this study be used to guide antifungal therapy in patients with raised titres? Antifungal therapy can reduce mortality in trauma patients with occult invasion[32]. Any marker that allows the initiation of early anticandidal and/or antibacterial therapy should provide the best chance of successful outcome. Rather than waiting for culture evidence of *Candida* invasion, we recommend that titres be measured early in high-risk patients and that systemic antifungal therapy be initiated for titres of 1:4 or greater. The authors' institution (Tampa General Hospital) is currently involved in a prospective placebo-controlled double-blind study to determine the efficacy of early systemic antifungal therapy in patients with raised titres and no overt evidence of fungal invasion. We believe that raised *Candida* antigen titres predict outcome in severely injured patients and that early therapy is one way in which to maximize the chances of a successful therapeutic outcome.

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Role of macrophage overactivation in the development of acute pancreatic injury in rats

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Background An increase in systemic inflammatory mediators from stimulated leucocytes and macrophages has been noted during acute pancreatitis. The role of cytolytic inflammatory macrophages and potential mechanisms in the development of acute pancreatic injury and endothelial barrier dysfunction are less well defined.

Methods Rats were challenged by an intraperitoneal injection of cytolytic or non-cytolytic inflammatory macrophage stimulators at various concentrations. The effects of oxygen free radicals, prostaglandin and extracellular calcium influx on macrophage-associated pancreatic endothelial compromise, measured by pancreatic intravascular plasma volume, pancreatic interstitial fluid volume, and the pancreatic extravascular human serum albumin distribution volume, were explored.

Results Zymosan-induced overactivation of cytolytic inflammatory macrophages resulted in the development of acute pancreatic endothelial dysfunction in a dose- and time-dependent pattern. An increase in pancreatic water content and interstitial fluid volume was observed following a higher dose (0·5 mg/g) of concanavalin A without alteration in plasma lipase level, while thioglycollate medium did not compromise pancreatic endothelial barrier function. Oxygen free radicals, but also prostaglandins and extracellular calcium influx, seemed to be involved in macrophage overactivation-induced pancreatic injury.

Conclusion Overactivation of cytolytic macrophages plays a role in the pathogenesis of pancreatic injury by initiating the development of endothelial barrier dysfunction. Multiple inflammatory mediators from overactivated macrophages act as intercellular signals between macrophages and the endothelium during acute pancreatic injury.

The development of acute pancreatic injury has been considered to be associated with uncontrolled liberation and activation of pancreatic enzymes and with pancreatic microcirculatory alterations[1–6]. Impairment of the pancreatic microcirculation following pancreatic ischaemia and the generation of oxygen free radicals are also involved in the pathogenesis of pancreatic injury. Alterations in pancreatic capillary number and endothelial permeability characterize severe pancreatic injury[7] The destruction of pancreatic capillary endothelial barrier function may be followed by an increase in capillary permeability, concomitant tissue oedema and injury, organ dysfunction and/or the formation of microthrombi, stasis and sludge of blood cells[8–10].

Another phenomenon probably associated with the development of acute pancreatic injury is the extensive infiltration of inflammatory leucocytes into the interstitial spaces[4] and the overproduction of oxygen free radicals noted in the early stage of acute experimental pancreatitis[11]. Systemic and/or pancreatic leucocytes and macrophages may be overactivated by the challenge and migrate into inflammatory foci, resulting in overproduction of inflammatory mediators and disturbance in the pancreatic endothelial barrier. To evaluate the possibility that macrophage overactivation plays a role in pancreatic damage, rat macrophages were stimulated by an intraperitoneal injection of zymosan (ZMS) at various concentrations in the present study. The aims were: (1) to determine whether various concentrations of ZMS alter pancreatic endothelial barrier function as measured by tissue water content, intravascular plasma volume, extravascular albumin volume, and interstitial fluid volume and if pancreatic function monitored by plasma levels of pancreatic enzymes is influenced; (2) to compare the effects of stimulators of cytolytic (ZMS and concanavalin A (CCA)) and non-cytolytic (thioglycollate medium; TM) inflammatory macrophages on pancreatic injury; and (3) to explore possible mechanisms of macrophage hyperactivation-induced pancreatic compromise, such as involvement of oxygen free radicals, prostaglandin, calcium influx and nitric oxide, by intravenous pretreatment with inhibitors of these factors.

Materials and methods

Animals

Adult male Sprague–Dawley rats (Mollegaard, Skensved, Denmark), weighing between 250 and 270 g, were fed standard rat chow (R_1; Astra-Evos, Sodertalje, Sweden) and had free access to water The animals were allowed to acclimatize to laboratory conditions for 4–6 days. They were kept in stainless steel mesh cages (three rats per cage) with a 12-h day/night cycle at a constant temperature of 22°C. The protocol was approved by the university animal ethics committee. All animals were handled in accordance with the guidelines of the Swedish Physiological Society

Preparation of the macrophage-stimulating solutions

ZMS, CCA and TM (Sigma Chemical, St Louis, Missouri, USA) were suspended in liquid paraffin (Sigma) by high-frequency vibration using an ultrasonic mixer (Optilab-BO; Philip Instrumentation, Stockholm, Sweden) to a final volume of 4 ml The suspensions were sterilized by incubation in a water bath at 100°C for 60 min and cooled at room temperature.

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Experimental protocol

In the first experiment, the animals were randomly allocated into four groups which received: (1) an intraperitoneal injection of paraffin alone (controls); (2) an intraperitoneal injection of ZMS suspension 0·25 mg per g body-weight; (3) ZMS 0·50 mg/g; and (4) ZMS 0·75 mg/g, to evaluate the influence of various doses of ZMS on the pancreatic endothelial barrier and plasma levels of lipase. Six animals in each group were killed 3, 6, 12 and 24 h after intraperitoneal challenge, except for the group given 0·75 mg ZMS (no animals survived for 24 h).

In the second experiment, stimulators of both cytolytic (ZMS and CCA) and non-cytolytic (TM) inflammatory macrophages were used at doses of 0·25 and 0·50 mg per kg body-weight. The animals were killed 24 h after the intraperitoneal injection.

The aim of the third experiment was to explore potential mechanisms by which macrophage hyperactivation induced by the intraperitoneal injection of ZMS 0·5 mg per g body-weight influenced pancreatic function. To evaluate potential effects of inflammatory mediators on ZMS-associated pancreatic injury, *N*-acetyl-L-cysteine (NAC, a 'broad' antioxidant and precursor in the biosynthesis of glutathione[12,13]), dimethyl sulphoxide (DMSO; a hydroxyl radical scavenger[14]), indomethacin (a cyclo-oxygenase inhibitor[15]), verapamil (a phenylalkylamine-type calcium channel antagonist[16]) or allopurinol (a xanthine oxidase inhibitor[17]) were used. The animals were pretreated by an intravenous injection (tail vein) of 1 ml of a solution containing either NAC (Sigma; 0·2 mg per g body-weight), DMSO (Sigma, 0·1 mg/g), indomethacin (Sigma; 0·04 mg/g), verapamil (Sigma; 0·004 mg/g) or allopurinol (Sigma; 0·16 mg/g) 1 h before the intraperitoneal injection of paraffin with ZMS. Plasma levels of pancreatic lipase and endothelial permeability were measured in all animals during the experimental period.

Evaluation of pancreatic endothelial permeability

The rats were anaesthetized by ether and both kidney pedicles were ligated through flank incisions Catheters were inserted into the femoral artery (outside diameter 0·75 mm; Portex, Hythe, UK) and vein (0·94 mm; Dow Corning, Detroit, Michigan, USA) to inject isotopes and for the subsequent collection of blood samples. A mixed solution of 1 ml ^{125}I-radiolabelled human serum albumin (HSA; Institutt for engergiteknikk, Kjeller, Norway) and ^{51}Cr-radiolabelled ethylenediamine tetra-acetic acid (EDTA) (NEN Research Products, Stockholm, Sweden) at a dose of approximately 10^6 c.p.m. and 10^5 c.p.m. respectively was injected through the femoral vein catheter. Some 50 min after the injection of ^{125}I and ^{51}Cr, 1 ml of a solution of ^{131}I-radiolabelled HSA with approximately 10^6 c.p.m. was injected intravenously and 5 min was allowed for intravascular distribution; 0·5 ml arterial blood was taken through the femoral artery catheter, after which the rats were killed by cervical dislocation. The pancreas was harvested and cleared of external blood. Radioactivity of the pancreas and blood plasma was measured in a γ-counter (1272 Clinigamma; LKB, Wallac, Finland) and the organ samples were weighed (wet weight), then dried at 60°C for 1 week and weighed again (dry weight).

In vivo endothelial permeability in the pancreas was assessed by the 60-min passage of ^{125}I-radiolabelled HSA and ^{51}Cr-radiolabelled EDTA from blood and by the 5-min circulation of ^{131}I-radiolabelled HSA as a 'reference' to pancreatic intravascular plasma volume, pancreatic interstitial fluid volume and the pancreatic extravascular HSA distribution volume as described previously[10] Pancreatic oedema was evaluated by pancreatic tissue water content, calculated as [(pancreatic wet weight − dry weight)/wet weight] × 100. Pancreatic intravascular plasma volume was calculated as: counts ^{131}I-labelled HSA per g tissue/counts ^{131}I-labelled HSA per ml plasma. Since ^{131}I-labelled HSA was circulating in blood only for 5 min, extravasation is considered negligible as compared with that of ^{125}I-labelled HSA. Pancreatic interstitial fluid volume was calculated as [counts ^{51}Cr-labelled EDTA per g tissue/counts ^{51}Cr-labelled EDTA per ml plasma] minus pancreatic intravascular plasma volume. Pancreatic extravascular albumin volume was calculated as [counts ^{125}I-labelled HSA per g tissue/counts ^{125}I-labelled HSA per ml plasma] minus pancreatic intravascular plasma volume. Extravascular albumin volume is useful for documenting the extravascular albumin content of the tissues relative to the readily measurable plasma albumin concentration without direct measurement of the more uncertain concentrations of albumin in the interstitial fluid; it provides a means of reflecting endothelial permeability in the various tissues during the experiment.

Isotope separation

Because of the high overlap between the γ emission spectra of ^{51}Cr and ^{131}I, the separation of these two isotopes was measured *in vitro*. Window settings were derived empirically so that the spillover from one channel to the other was minimized as described previously[9] The window settings were 240–400 keV for ^{51}Cr, 260–470 keV for ^{131}I and 15–75 keV for ^{125}I. ^{51}Cr and ^{131}I standards were counted for every experiment to obtain spillover corrections. Counts were corrected for background and spillover, for the influence of sample volume on counting efficiency and spillover, and for ^{131}I radioactive decay during the period of measurement. The tubes loading the solution of ^{51}Cr-labelled EDTA and ^{131}I-labelled HSA were measured before and after injection to determine the total counts injected in order to calculate whole body interstitial fluid volume and plasma volume.

Statistical analysis

Data were expressed as mean(s.e.m.). Student's *t* test was used to compare means of two groups following analysis of variance for multiple comparison between groups. A non-parametric test (Mann–Whitney *U* test) was used for comparing the values calculated from radioactivity measurements of two groups. Differences were considered significant at *P* values less than 0·05.

Results

Pancreatic water content increased significantly from 6 h after 0·25 mg ZMS per g body-weight, 3 h after 0·5 mg ZMS and 1 h after 0·75 mg ZMS (*Table 1*). A significant decrease in pancreatic intravascular plasma volume was

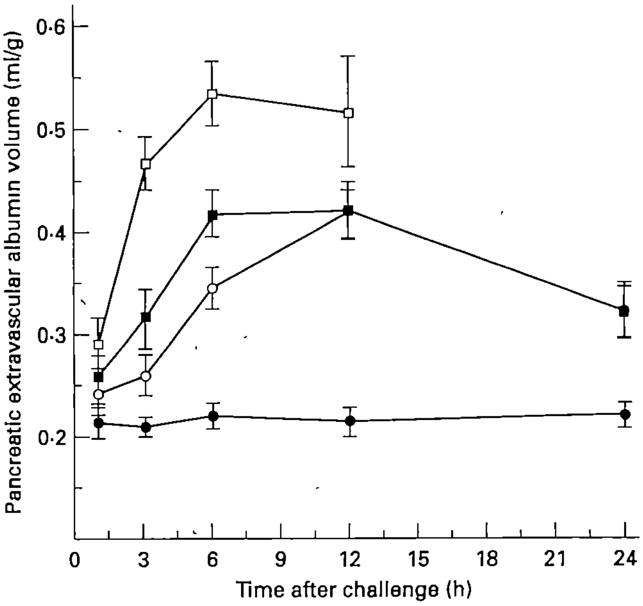

Fig. 1 Mean(s.e.m.) pancreatic extravascular albumin volume in animals with intraperitoneal administration of 4 ml paraffin (●), or intraperitoneal zymosan in doses of 0·25 (○), 0·50 (■) and 0·75 (□) mg per g body-weight

Table 1 Effect of zymosan on pancreatic water content, intravascular plasma volume and interstitial fluid volume

	Time after challenge			
	1 h	6 h	12 h	24 h
Pancreatic water content (%)				
Controls	70·0(0·6)	70·2(0·5)	70·6(0·7)	70·5(0·8)
ZMS 0·25	71·0(1·0)	74·1(0·7)	74·2(0·8)	71·8(0·7)
ZMS 0·50	72·4(1·2)	75·5(1·2)	74·1(0·8)	72·1(0·9)
ZMS 0·75	78·0(1·0)	77·0(1·2)	72·2(1·1)	–
Pancreatic intravascular plasma volume (ml/g)				
Controls	0·064(0·008)	0·060(0·006)	0·065(0·007)	0·064(0·008)
ZMS 0·25	0·064(0·010)	0·066(0·006)	0·042(0·007)	0·051(0·007)
ZMS 0·50	0·060(0·007)	0·060(0·008)	0·048(0·006)	0·056(0·007)
ZMS 0·75	0·055(0·007)	0·043(0·005)	0·051(0·006)	–
Pancreatic interstitial fluid volume (ml/g)				
Controls	1·965(0·090)	2·010(0·070)	1·975(0·080)	1·985(0·060)
ZMS 0·25	1·984(0·080)	2·406(0·060)	2·493(0·070)	2·241(0·050)
ZMS 0·50	2·154(0·080)	2·852(0·090)	2·643(0·060)	2·574(0·50)
ZMS 0·75	2·305(0·080)	2·483(0·050)	2·330(0·006)	–

Values are mean(s.e.m.) Controls received an intraperitoneal injection of 4 ml paraffin Other groups received intraperitoneal zymosan (ZMS) at a dose of 0·25, 0·50 or 0·75 mg per g body-weight

noted in animals receiving 0·25 and 0·5 mg ZMS at 12 and 24 h, and in animals given 0·75 mg from 1 h onwards compared with controls (*Table 1*). Pancreatic extravascular albumin volume and interstitial fluid volume were significantly increased in animals administered 0·25 mg from 6 h, 0·5 mg from 3 h, and 0·75 mg from 1 h, compared with controls (*Table 1, Fig. 1*).

The effect of the various macrophage stimulators on pancreatic endothelial barrier integrity 24 h after challenge is shown in *Table 2*. Pancreatic water content significantly increased in animals administered both 0·25 and 0·5 mg ZMS per g body-weight or 0·5 mg CCA per g body-weight compared with controls. A significant decrease in pancreatic intravascular plasma volume and increase in pancreatic extravascular albumin volume were noted only in animals challenged with ZMS. The interstitial fluid volume was significantly higher in animals treated with ZMS or with 0·5 mg CCA. No difference was seen in animals given TM compared with controls.

Pancreatic water content, intravascular plasma volume, extravascular albumin volume and interstitial fluid volume in ZMS-challenged animals pretreated with NAC differed significantly from that in ZMS-challenged animals with saline pretreatment, but not from that in animals receiving paraffin alone (*Fig 2, Table 3*). Pancreatic water content, extravascular albumin volume and interstitial fluid volume in ZMS-challenged animals pretreated with DMSO or indomethacin were significantly higher and intravascular plasma volume was lower than that in paraffin-challenged and saline-pretreated animals, while significantly different from that in ZMS-challenged animals with saline pretreatment. The values in ZMS-challenged animals with allopurinol pretreatment were significantly higher than those in animals receiving saline alone, but not different from those in ZMS-challenged animals pretreated with saline. In ZMS-challenged animals with verapamil pretreatment, water content was significantly increased and intravascular plasma volume decreased compared with animals given saline, while extravascular albumin and interstitial fluid volume values differed significantly from those in both saline- and ZMS-challenged animals with saline pretreatment.

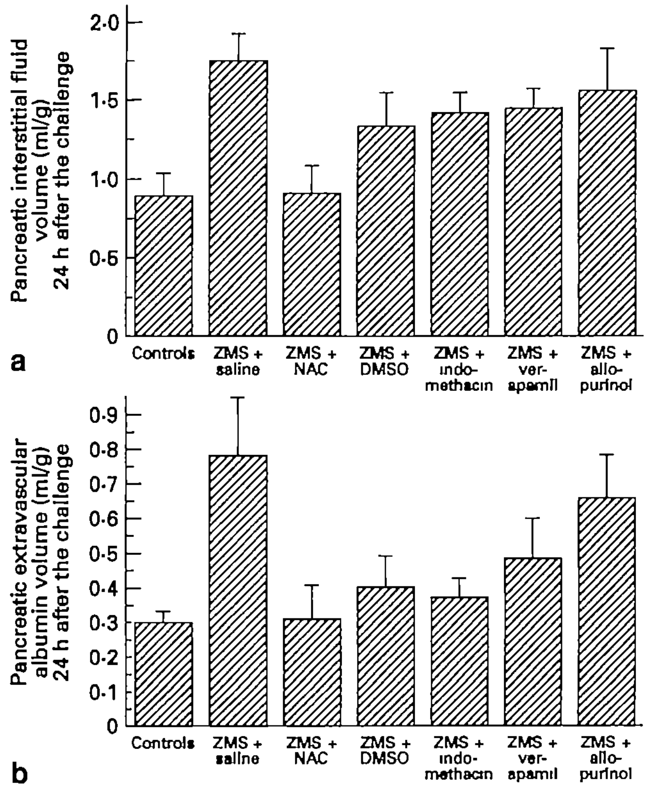

Fig. 2 Mean(s.e.m.) pancreatic a interstitial fluid volume and b extravascular albumin volume in animals with intraperitoneal administration of 4 ml paraffin (controls), or intraperitoneal injection of zymosan (ZMS) 0·25 mg per g body-weight together with intravenous preadministration of saline, *N*-acetyl-L-cysteine (NAC), dimethyl sulphoxide (DMSO), indomethacin, verapamil or allopurinol

Plasma lipase levels were significantly increased at 12 and 24 h after the administration of 0·25 mg ZMS, from 6 h after 0·5 mg ZMS, and from 3 h after 0·75 mg ZMS (*Fig. 3*). When comparing the effects of ZMS, CCA and

Table 2 Effect of zymosan, concanavalin A and thioglycollate medium on pancreatic water content, intravascular plasma volume, interstitial fluid volume and extravascular albumin volume

	Pancreatic water content (%)	Pancreatic intravascular plasma volume (ml/g)	Pancreatic interstitial fluid volume (ml/g)	Pancreatic extravascular albumin volume (ml/g)
Controls	67·6(1·4)	0·067(0·005)	0·909(0·100)	0·299(0·024)
ZMS 0·25	71·2(1·9)	0·041(0·001)	1·382(0·037)	0·351(0·015)
CCA 0·25	70·3(1·7)	0·073(0·005)	1·055(0·241)	0·267(0·007)
TM 0·25	64·4(1·2)	0·061(0·006)	1·015(0·052)	0·298(0·006)
Controls	68·2(1·8)	0·065(0·004)	0·904(0·086)	0·289(0·035)
ZMS 0·50	71·4(4·8)	0·048(0·003)	1·455(0·102)	0·416(0·026)
CCA 0·50	71·6(5·8)	0·069(0·002)	1·178(0·241)	0·321(0·102)
TM 0·50	68·4(3·8)	0·063(0·007)	1·112(0·286)	0·329(0·215)

Values are mean(s.e.m.). Controls had intraperitoneal administration of 4 ml paraffin. Other groups received zymosan (ZMS), concanavalin A (CCA) or thioglycollate medium (TM) at a dose of 0·25 or 0·50 mg per g body-weight

Table 3 Effect of intravenous preadministration of *N*-acetyl-L-cysteine, dimethyl sulphoxide, indomethacin, verapamil and allopurinol on zymosan-induced changes in pancreatic water content, intravascular plasma volume and plasma level of lipase

	Pancreatic water content (%)	Pancreatic intravascular plasma volume (ml/g)	Lipase (ukat/l)
Controls	69·1(1·7)	0·071(0·006)	1·5(0·3)
ZMS+saline	76·5(1·6)	0·037(0·003)	3·1(0·2)
ZMS+NAC	71·0(2·3)	0·069(0·005)	1·8(0·3)
ZMS+DMSO	73·3(2·0)	0·060(0·007)	2·0(0·2)
ZMS+indomethacin	74·5(0·5)	0·051(0·006)	2·0(0·4)
ZMS+verapamil	75·0(1·4)	0·041(0·007)	2·2(0·3)
ZMS+allopurinol	75·9(1·7)	0·033(0·004)	2·7(0·6)

Values are mean(s.e.m.) Controls had intraperitoneal administration of 4 ml paraffin. Other groups received intraperitoneal zymosan 0·25 mg per g body-weight ZMS, zymosan; NAC, *N*-acetyl-L-cysteine; DMSO, dimethyl sulphoxide

TM, a significant increase in plasma lipase level (at 24 h) was noted in animals receiving ZMS (mean(s.e.m.) 3·24(0·53) ukat/l at 0·25 mg ZMS *versus* 1·56(0·24) ukat/l for controls and 5·56(0·68) ukat/l at 0·50 mg *versus* 1·45(0·22) ukat/l for controls). There was no significant difference between animals challenged with CCA or TM and controls. Preadministration of NAC and DMSO significantly improved alterations in plasma levels of lipase induced by ZMS (*Table 3*).

Discussion

The results of the present study imply that ZMS-induced macrophage overactivation causes alterations in pancreatic endothelial barrier injury. ZMS is an inflammatory stimulator derived from yeast cell walls and is a stimulant of cytolytic inflammatory macrophages, directly activating leucocytes and macrophages both *in vivo* and *in vitro*[18,19]. Mechanisms that may explain the effect of ZMS on macrophages include that ZMS is

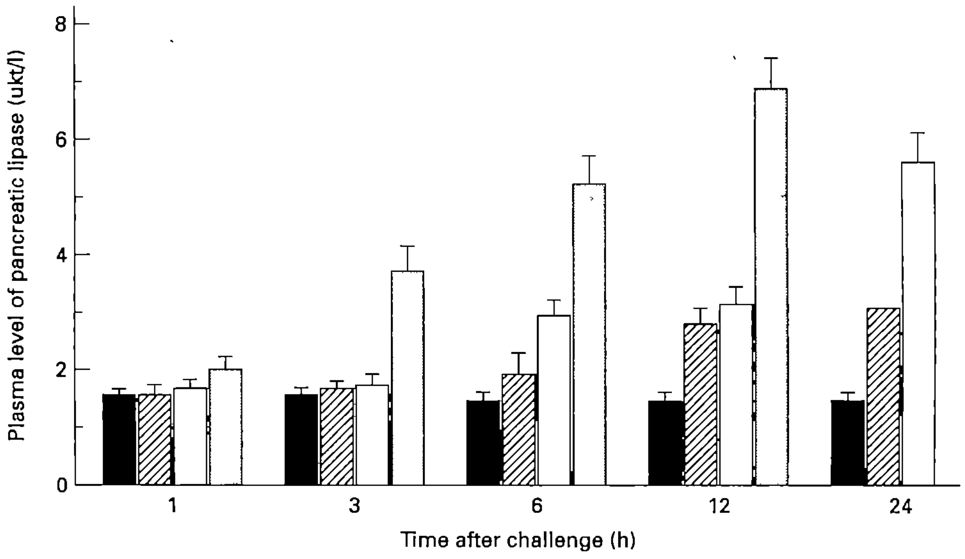

Fig. 3 Mean(s.e.m.) plasma levels of pancreatic lipase in animals with intraperitoneal administration of 4 ml paraffin (■) or intraperitoneal zymosan in doses of 0·25 (▨), 0·50 (□) and 0·75 (□) mg per g body-weight

opsonized with serum components, strongly stimulates glucose metabolism via the hexose monophosphate shunt and complement activation (Fc) by the alternative pathway, and triggers macrophage activation. Intraperitoneal administration of ZMS suspension induced pathological alterations in both intraperitoneal and extraperitoneal organs, e.g. the intestine and the lungs, characterized by increased barrier permeability, structural and functional damage, and organ failure[20,21], probably due to the release of cytokines, oxygen free radicals, an increase in tissue lipid peroxides, activation of myeloperoxidase, raised adherence capacity of neutrophils on endothelial cells, and alteration in cytosolic calcium concentration. In the present study, it was found that the pattern of ZMS-induced pancreatic injury appeared to be dose-dependent, as shown by the observation that the development of pancreatic endothelial dysfunction was most pronounced in the early stage after a higher dose of ZMS than after a lower dose.

The aetiology of experimental pancreatitis has been ascribed to: (1) an increase in pancreatic duct pressure and bile reflux into the pancreatic tissue (closed duodenal loop, pancreatic duct obstruction and bile salt ductal perfusion); (2) enteral nutritional disorders (dietary ethionine supplementation, choline-deficient diet and parenteral nutrition); (3) traumatic injury to the pancreas (crushing, clamping or puncturing of the pancreatic gland, and pancreatic ischaemia and reperfusion); and (4) immunological injury of the pancreas (injection of Forssman antibodies)[22,23]. In humans, however, pathogenetic alterations and possible mechanisms in acute pancreatitis are not yet fully clarified[24]. In previous experimental studies on the effect of septic challenges on endothelial barrier function in multiple organs and tissues, it was found that pancreatic endothelial barrier permeability significantly increased after various challenges[25]. These types of challenge may induce microcirculatory injury and organ failure probably by altering macrophage activation[26]. The present study shows that direct stimulation of macrophages results in an increase in pancreatic water content, extravascular protein volume and interstitial fluid volume and a decrease in intravascular plasma volume, indicating that the overactivation of macrophages could play an important role in the pathogenesis of pancreatic injury. Macrophage overactivation probably induces pancreatic injury by increasing pancreatic endothelial barrier permeability, plasma leakage and oedema formation, and concomitant organ dysfunction, since raised plasma lipase levels were noted after the occurrence of pancreatic endothelial barrier dysfunction following challenge with various doses of ZMS. Pancreatic endothelial permeability seemed reversible 24 h after ZMS, since the levels of parameters for endothelial permeability at 24 h were lower than at 12 h. Possible explanations are that pancreatic endothelial barrier integrity may start to recover from challenge-induced damage or pancreatic interstitial pressure may be so high that leakage of the markers is resisted. When comparing alterations in endothelial barrier permeability in various organs after challenge with cytolytic inflammatory macrophage stimuli, it was noted that the occurrence of endothelial barrier dysfunction was in the sequence of pancreas, kidneys, liver and intestine.

To investigate potential mechanisms whereby macrophage overactivation induces pancreatic injury, other macrophage stimuli were analysed in the present study: CCA, a plant lectin acting on cytolytic inflammatory macrophages, phagocytic function and particle internalization by C_1 complement; and TM, a stimulus of non-cytolytic inflammatory macrophages which alters macrophage metabolic activity and elicits polymorphonuclear leucocytes, macrophages and lymphocytes. An increase in pancreatic water content and interstitial fluid volume was observed following a higher dose (0·5 mg/g) of CCA without alteration in plasma lipase level, while TM did not compromise pancreatic endothelial barrier function. Although both ZMS and CCA are stimuli of cytolytic inflammatory macrophages, their biological properties are obviously different, which may explain the different effects of ZMS and CCA on the initiation of pancreatic injury. Previous studies have shown that the response of reactive oxygen metabolites induced by ZMS was significantly and rapidly amplified as compared with CCA[27]. It may be that the release of inflammatory mediators induced by ZMS is rapidly amplified, initiating the development of pancreatic injury or that ZMS promotes increased intercellular adhesion molecule 1 expression on the vascular endothelium through the cytokine-primed pathway and induces CD11/CD18 expression on circulating leucocytes via a neutrophil-dependent pattern[28].

Acute pancreatitis is associated with reduction in pancreatic blood flow, increased capillary permeability, vascular leakage, poor capillary filling, and congestion and stasis of the capillary circulation, followed by the occurrence of systemic complications and the development of multiple organ dysfunction. Although it is still controversial whether alterations in pancreatic capillary endothelial barrier function cause acute pancreatitis or occur as a consequence of the pancreatitis, pancreatic microcirculatory endothelial barrier dysfunction plays a role in the pathogenesis of acute pancreatitis and pancreatitis-induced multiple organ injury[9]. The results from the present study imply that compromised endothelial barrier integrity may initiate pancreatic injury induced by ZMS-related overactivation of macrophages. Pretreatment with NAC prevented macrophage overactivation-induced endothelial barrier dysfunction, while pretreatment with DMSO, indomethacin or verapamil was only partly protective. Allopurinol pretreatment failed to prevent macrophage overactivation-induced pancreatic endothelial barrier injury. These results indicate that macrophage overactivation compromises pancreatic endothelial barrier integrity mainly through the release of oxygen free radicals, and that hydroxyl radicals are partly involved in the pathophysiology of endothelial damage, since NAC as a 'broad' oxygen free radical scavenger inactivates both hypochlorous acid and hydroxyl radicals, while DMSO neutralizes only hydroxyl radicals[12]. Prostaglandins and extracellular calcium influx may also partly be associated with pancreatic endothelial dysfunction following macrophage overactivation. The finding that pretreatment with NAC, DMSO, indomethacin and verapamil prevented an increase in plasma lipase level implies that oxygen free radicals, prostaglandins and extracellular calcium influx may to different degrees be involved in pancreatic acinar injury. Further experiments on the effect of cytolytic inflammatory macrophage overactivation on acute pancreatic injury should be encouraged to eliminate the limitations of the techniques used.

In conclusion, ZMS-induced overactivation of cytolytic inflammatory macrophages resulted in the development of acute pancreatic endothelial barrier dysfunction in a dose-

and time-dependent pattern. Oxygen free radicals play an important role in the pathogenesis of macrophage overactivation-induced pancreatic endothelial injury, together with the involvement of prostaglandins and extracellular calcium influx. The results from the present study imply that macrophage overactivation may play a role in the pathogenesis of acute pancreatic injury.

Acknowledgements

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Reoperative surgery for choledochal cysts

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Background Complications often follow if a choledochal cyst is treated simply by drainage, either internal or external. This study reviews 17 patients who had had previous cystoenterostomy ($n = 9$) or external drainage ($n = 8$) and who required reoperation and cyst excision.

Methods The study was a retrospective review including ten women and seven men managed over 9 years. The indications for reoperation were stone formation (10 patients), pancreatitis (three), portal hypertension (two) and hepatic abscess (one); two patients were asymptomatic.

Results Definitive surgery with cyst excision was possible in all patients who had previously had external cyst drainage and in seven of nine who had had previous cystoenterostomy. There were no deaths. Two postoperative biliary leaks and two duodenal fistulas resolved spontaneously.

Conclusion Excision of a choledochal cyst is possible and desirable even after a previous drainage operation. In severely ill patients with a complication of choledochal cyst, external drainage may be a preferable initial manoeuvre.

Choledochal cysts are best managed by total excision, although in the past internal drainage into the jejunum or duodenum has been recommended[1–5]. Internal drainage is often associated with anastomotic narrowing because of various factors, including lack of a proper mucosal lining in the cyst and recurrent infection and inflammation due to reflux of pancreatic enzymes[6–8]. Reoperation may be necessary to excise this choledochal cyst. Revisional surgery is complicated by adhesions and by the sequelae of inadequate biliary drainage, some of which, such as malignancy, may even be fatal. This article reviews an experience with reoperative surgery for choledochal cysts following previous cyst drainage operations. The presentation, problems and difficulties encountered during surgery were studied.

Patients and methods

Sixty-nine patients had surgery for choledochal cysts at this hospital in the 9 years from 1987 to 1995. Seventeen (25 per cent) had had a previous cyst drainage operation The records of these patients were reviewed. Ten women and seven men of mean age 36 (range 16–52) years had their initial operation performed 6 months to 11 years (mean 2·9 years) before presentation. Eight patients had undergone external drainage of the choledochal cyst, six had had choledochocystojejunostomy and three had received a choledochocystoduodenal anastomosis.

Ultrasonography was done in all patients and barium meal examination was performed in those who had previously had cyst drainage into the duodenum. All patients had upper gastrointestinal tract endoscopy to look for oesophageal varices. Cholangiography through the drainage catheter was performed in patients who had had external drainage and the remaining patients underwent endoscopic retrograde cholangiopancreatography (ERCP)

The cysts were grouped according to Todani *et al*'s modification of Alonso Lej's classification[1]: type I, solitary extrahepatic cyst; type II, extrahepatic supraduodenal diverticulum; type III, choledochocoele; type IVa, extrahepatic and intrahepatic cysts; type IVb, multiple extrahepatic cysts; and type V, Caroli's disease.

Regular follow-up was carried out after surgery to assess postoperative morbidity, regression in size of intrahepatic cysts, recurrence of cholangitis and other features of biliary obstruction.

Results

External drainage of the choledochal cyst had been performed in eight patients, of whom three had extensive pericystic adhesions making the excision difficult; two patients had perforation of the cyst with biliary peritonitis and in three the cyst was mistaken for duct dilatation secondary to choledocholithiasis and T tube drainage had been performed.

Nine patients had had previous cystoenteric drainage operations; two were asymptomatic. Presenting complaints in the seven symptomatic patients were abdominal pain, jaundice and recurrent attacks of cholangitis. Portal hypertension was suspected in two patients who had cystoenteric drainage done 3 and 5 years earlier and had been jaundiced for about 9 months before admission. Three patients had raised serum amylase levels after episodes of acute epigastric pain. Surgical excision of the cysts was advised, even in the asymptomatic patients, after discussion of the possible long-term complications.

Ultrasonography revealed a dilated bile duct in all patients; ten had calculi in the cyst and one had a large abscess in the left lobe of the liver. In the patients with portal hypertension there was no evidence of thrombosis or compression of the portal vein. Three of the six patients with a choledochocystoduodenostomy had a barium meal investigation; the contrast entered the cyst in only one patient.

Upper gastrointestinal endoscopy showed oesophageal varices in both patients with portal hypertension. Based on tube cholangiography and ERCP findings, nine patients were thought to have a type I cyst, seven had type IVa cysts (cystic–cystic in five patients and cystic–cylindrical in two) and one had type IVb cysts.

The pancreatic duct could be evaluated in 12 patients, of whom three had an abnormal pancreatic biliary duct junction. ERCP was carried out in patients with previous cystoenteric drainage. In all but one no contrast was seen to enter the bowel, indicating anastomotic stenosis; this included the two asymptomatic patients. Calculi were

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evident in eight patients who had had internal drainage and two with external drainage (*Fig. 1*).

At operation, mobilization of the cyst was complicated by pericystic adhesions especially in patients with a previous choledochocystoduodenostomy; the entire hepatoduodenal ligament in these patients was inflamed with dense vascular adhesions around the choledochal cyst. The duodenum around the cyst–duodenal anastomosis was also involved in the inflammatory response. The anastomosis between the cyst and the bowel was either blocked completely or reduced to a small lumen with multiple stones packed in the cyst. Separation of the cyst from the portal vein was difficult. Two patients with choledochocystojejunostomy had pericholedochal varices due to portal hypertension. Excision of the cyst was possible in only one; in the other a portasystemic shunt was planned but could not be done because of intraoperative hypotension.

The surgical procedure was comparatively easier in patients who had had previous external drainage. Total excision of the cysts was possible in all eight cases. Cyst excision was achieved in seven of the nine patients who had previously had internal drainage. In the patient with a cholangitic abscess in the left lobe of the liver, cyst excision was performed following ultrasonographically guided drainage of the liver abscess. Excision was not possible in one patient with pericystic adhesions and in one with portal hypertension. External drainage of the cyst was done in the former patient and a cyst excision is proposed in the near future in the latter, a wide cystojejunal drainage was performed.

There was no operative mortality. After operation two patients had a bile leak which persisted for 12–26 days and closed spontaneously. Two patients with previous choledochocystoduodenostomy had duodenal fistulas, which also settled with conservative management. Secondary biliary cirrhosis was seen in the liver biopsy of both patients with portal hypertension but oesophageal varices regressed 6 months after cyst excision in one of these patients. On follow-up, a reduction in the size of intrahepatic cysts was seen on ultrasonography in two (both of cystic–cylindrical type) of the five patients with type IVa cysts whose extrahepatic cysts could be excised. No patient required readmission.

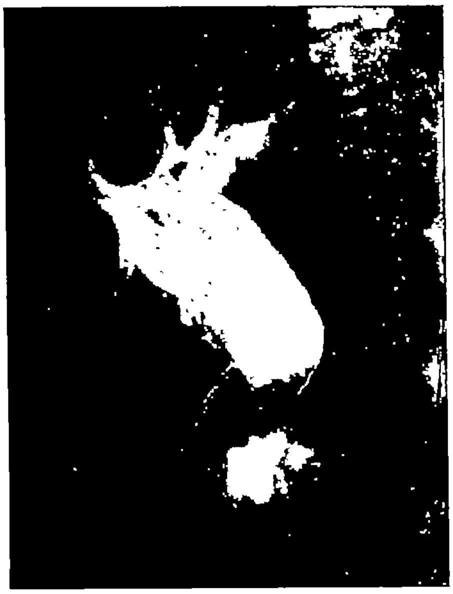

Fig. 1 Tube cholangiogram showing a choledochal cyst containing multiple calculi

Discussion

The surgical treatment of choledochal cysts has changed: drainage of the cyst into the duodenum was replaced by Roux-en-Y choledochocystojejunostomy. Presently, excision of the cyst is the most frequently performed procedure. Internal drainage is associated with a high rate of cystoenteric anastomotic stenosis; 13–69 per cent of patients need reoperation for abdominal pain, jaundice and recurrent cholangitis[4–9]. The majority of these patients are adult and need revisional surgery in the form of excision of the choledochal cyst to provide adequate biliary drainage. There are only a few reports in the literature highlighting the difficulties encountered in managing such patients[9–13]. Biliary obstruction due to a blocked cystoenteric anastomosis may lead to cystolithiasis, cholangitic liver abscess, portal hypertension due to secondary biliary cirrhosis, malignancy and pancreatitis (*Table 1*).

The anastomosis in all the present patients (including the two asymptomatic ones) who had had internal drainage operations was either completely blocked or grossly stenosed; most had calculi in the cyst. Other reports also document a high incidence of cystolithiasis in patients who have undergone previous drainage operations[12]. These calculi can cause liver abscesses, as seen in one of the present patients in whom the calculi extended to the intrahepatic ducts.

Calculi in the cyst have also been blamed for the development of malignancy; Flanigan[14] found a high incidence of calculi in patients with malignancy. It is estimated[5] that the risk of developing malignancy in the retained cyst may be as high as 50 per cent. In a review of 16 patients who had revisional surgery, Todani *et al.*[10] noted three in whom malignancy developed in a retained cyst. Nagorney and colleagues[9] treated eight patients with malignancy associated with a choledochal cyst, five of whom had had one or more cyst-related operations before malignancy was detected. These tumours are not resectable and the majority of patients die soon after the diagnosis is established[15].

Another serious complication of prolonged biliary obstruction is the development of secondary biliary cirrhosis and portal hypertension, as seen in two patients in this series. The cyst could be excised in only one; large pericholedochal varices rendered excision difficult in the second patient. A portasystemic shunt is necessary before excision can be attempted[4]. Reversal of secondary biliary cirrhosis has been reported with drainage of the choledochal cyst[16]. Because of the possibility of portal hypertension, upper gastrointestinal endoscopy should always be performed in patients who have had a previous cyst drainage operation so that adequate preparation can be made for constructing a portasystemic shunt.

Pancreatitis is also more likely in patients who have had internal drainage operations, because the abnormal lower end of the cyst continues to cause reflux into the pancreatic duct. In one study[17], 80 per cent of patients had pancreatitis. Recurrence of pancreatitis can be prevented by excision of the cyst.

In the present authors' experience, excision of the choledochal cyst was most difficult in patients who had

Table 1 Indications for reoperative surgery following internal drainage procedures for choledochal cysts

Reference	Year	No. of patients	Indication for reoperation	Nature of reoperation
Takiff *et al.*[12]	1985	12 (16 operations)	Cholangitis (14) Pain and jaundice (1) Recurrent pain (1)	Excision (5) Bilioenteric drainage procedure (11)
Todani *et al.*[10]	1988	8	Cholangitis (5) Malignancy (3)	Excision and hepaticoduodenostomy (3) Excision and Roux hepaticojejunostomy (3) Palliative bypass alone (1) Laparotomy alone (1)
Tan and Howard[13]	1988	7	Cholangitis (5) Portal hypertension (2)	Excision (5) Cystojejunostomy (2)
Present series	1997	9	Pancreatitis (3) Cholangitis (2) Portal hypertension (2) Asymptomatic (2)	Excision (7) Cystojejunostomy (2)

Table 2 Experience with reoperation following external drainage of choledochal cysts

Reference	Year	No of patients	Indication for external drainage	Outcome after excision
Todani *et al.*[10]	1987	8	Severe cholangitis (4) Acute pancreatitis (1) Bile peritonitis (2) Indication (1)	Favourable
Tan and Howard[13]	1988	4	Cyst rupture (1) Cholangitis (3)	Favourable
Present series	1997	8	Pericystic adhesions (3) Mistaken diagnosis (3) Perforation of cyst (2)	Favourable

had previous drainage into the duodenum, and easiest in those who had had external drainage. In the former patients, the hepatoduodenal ligament was fibrosed and shortened with vascular adhesions; the duodenum was also involved in the inflammatory process. Patients with previous external drainage had adhesions around the track of the drain tube but the planes around the cyst could be dissected with ease. Although the drain is an avenue for extraneous infection, adequate biliary decompression prevents the development of cholangitis and secondary biliary cirrhosis. The choledochal cyst could be excised in all patients who had had external drainage, but in only seven of the nine who had internal drainage. In Todani *et al.*'s review[10], in all eight patients with external drainage excision was achieved with good results (*Table 2*), and of 19 patients with enteric drainage five underwent excision and in three only a palliative bypass could be performed because malignancy had developed. The remaining 11 patients were lost to follow-up. Patients who have revision surgery may have a higher incidence of bile leak after cyst excision than those who have primary cyst excision, possibly because proximal ducts are unhealthy as a result of cholangitis and calculi.

Cyst excision can be performed safely after a cyst drainage operation in the majority of cases. In severely ill patients, such as in the rare case of a cyst perforation, external drainage of the choledochal cyst is a safe option and secondary cyst excision can be done later. The presence of an external catheter ensures that the patient will return for definitive surgery.

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Case report

Pilonidal cyst of the breast

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Pilonidal disease is most commonly encountered in the anal cleft but it may occur in other hair-bearing sites[1,2]. The common aetiological pathway is an inflammatory response to hair with cystic change and bacterial superinfection. An unusual case is reported, following immediate breast reconstruction with a rectus abdominis myocutaneous free flap (TRAM flap).

Case report

Immediate breast reconstruction with a TRAM flap was carried out for a 12-mm grade 2 ductal carcinoma with associated ductal carcinoma *in situ*. Eight months later the patient presented with several firm indistinct 1-cm subcutaneous lumps on the superior aspect of the reconstructed breast, related to the subcutaneous de-epithelialized component of the TRAM flap. There was no evidence of associated lymphadenopathy and because imaging of the lesions was inconclusive an excision biopsy was performed. At operation the masses were noted to be in the fat, deep to the dermis of the de-epithelialized segment of the flap.

Histological examination (*Fig 1*) revealed a chronic inflammatory reaction in the dermis and subcutaneous tissue with multiple hair shafts surrounded by foreign body giant cells and occasional hair follicles, consistent with pilonidal cyst disease.

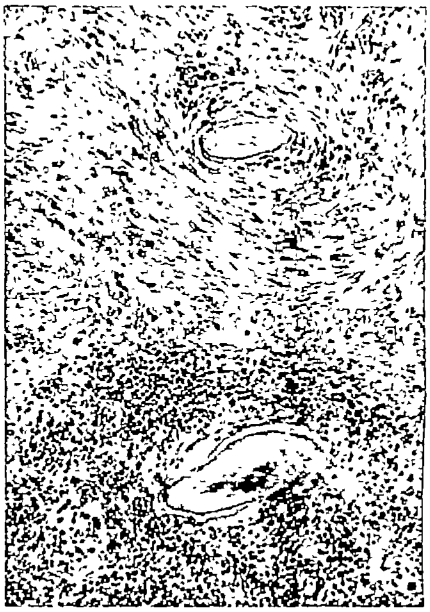

Fig. 1 Hair shaft fragments surrounded by foreign body giant cell reaction. (Haematoxylin and eosin stain, original magnification ×200)

Discussion

In TRAM flap reconstruction of the breast, an ellipse of full-thickness skin is retained to make good the tissue defect, the remaining flap being de-epithelialized to provide bulk for the reconstruction[3,4]. During the normal cycle of hair growth the follicles move deeper into the subcutaneous tissue after a hair has been shed. It is suggested that such follicles may remain viable in the flap following de-epithelialization and may thus develop into pilonidal cysts.

Although the commonest cause of lumps in such circumstances is fat necrosis[5] and local recurrence of the original tumour is also a possibility, pilonidal disease should be considered in the differential diagnosis of a lump in the breast reconstructed with a TRAM flap.

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British Journal of Surgery 1997, 84, 785

Case report

Complete pancreatic encasement of the proximal hepatic portal vein: a previously undescribed congenital anomaly

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Anomalous fusion of the ventral and dorsal pancreas may occur during embryonic development of the pancreas to produce pancreas divisum and, rarely, an annular pancreas[1-3]. The authors describe a new anomaly consisting of complete encirclement of the proximal hepatic portal and adjacent superior mesenteric vein.

Case report

A 59-year-old Asian man was referred to the Department of Surgery, Queen Elizabeth Hospital, following endoscopic stenting for obstructive jaundice. Endoscopy and biopsy confirmed a polypoid adenocarcinoma of the ampulla of Vater but pancreatography was not possible. Spiral contrast-enhanced computed tomography showed a bulky head of pancreas but no obvious tumour mass. A clear plane around the superior mesenteric artery was present but the superior mesenteric vein and proximal portal vein were not well defined (*Fig. 1a*).

At pancreatoduodenectomy the neck of the pancreas was dissected free from the superior mesenteric vein and the portal vein and transected. The cut surface of the pancreas was normal in size and there was a dilated main pancreatic duct. After separation of the uncinate process from the superior mesenteric vessels, the cephalic extension of the uncinate was found to be completely fused to the posterior aspect of the body of the pancreas over an area 4 × 0·6 cm. The confluence of the splenic vein with the superior mesenteric vein and the hepatic portal vein was completely encircled by pancreatic parenchyma (*Fig 1b*). The parenchymal extension of the uncinate process was divided from the body of the pancreas and the operation was completed uneventfully. There was no major pancreatic duct or major branch of the pancreatic ductal system in this abnormal parenchymal extension. The main tumour was 2·5 cm in diameter and the parenchyma of the head of the pancreas was not inflamed.

Discussion

The findings at operation, and also shown by retrospective examination of the computed tomographs, indicate a congenital anomaly of the pancreas encasing the proximal hepatic portal vein. During embryogenesis the ventral pancreas rotates to the right (6-mm embryo stage) and then to the left about the axis of the primitive gut to fuse posteriorly with the dorsal pancreas (7-mm embryo stage)[1-4]. Although an extreme left extension of the uncinate process of the ventral pancreas has been described, complete fusion with the dorsal pancreas to the left of the superior mesenteric vein and proximal hepatic portal vein has not been reported[4-5]. This anomaly could create an incorrect radiological diagnosis of dorsal pancreatic space tumour extension suggesting non-resectability and could lead to technical problems during surgery.

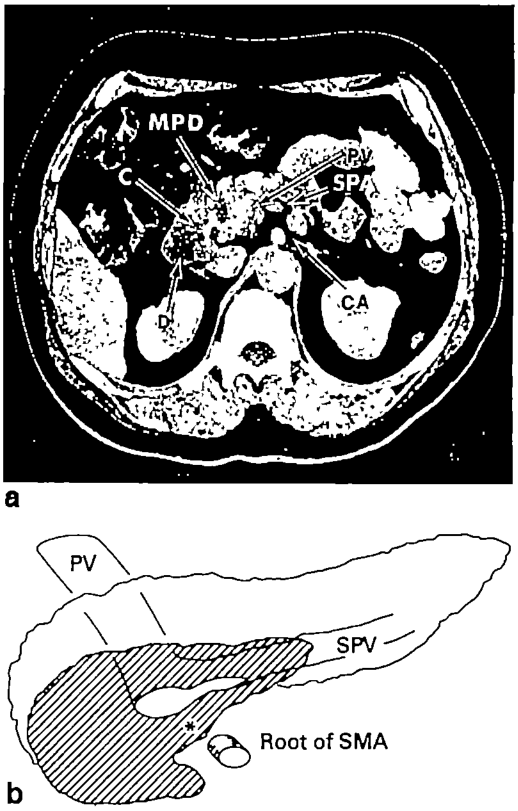

Fig. 1 a Contrast-enhanced spiral computed tomography demonstrating encasement of the hepatic portal vein (PV) by parenchyma. MPD, main pancreatic duct; C, stent in main bile duct; D, duodenal lumen; SPA, splenic artery; CA, coeliac axis. b Three-dimensional reconstruction of the anomalous fusion of pancreatic parenchymal tissue (*). PV, hepatic portal vein; SPV, splenic vein; SMA, superior mesenteric artery

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Bile duct injury following laparoscopic cholecystectomy: referral pattern and management

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Background Laparoscopic cholecystectomy is associated with a higher incidence of bile duct injury than open cholecystectomy. This study reviews the management of bile duct injury in a tertiary hepatobiliary unit.

Methods From 1991 to 1995, 27 patients (18 women) of median age 49 (range 25–67) years were referred to this unit with bile duct injury following elective laparoscopic cholecystectomy. Laparoscopic cholecystectomy was described as 'uneventful' in 14 and 'difficult' in 13 patients; six injuries were recognized at operation.

Results Patients were transferred a median of 26 (range 0–990) days after laparoscopic cholecystectomy, although initial symptoms were recorded a median of 3 (range 0–700) days after cholecystectomy. Fifteen patients underwent additional surgery before referral. Management before referral included surgical exploration (15 patients), endoscopic cholangiography (ERC) and stent insertion (three), external drainage of bile collections (five), and conservative management (five). Management after referral included surgical reconstruction (19 patients), laparotomy with drainage (one), percutaneous drainage (two), ERC and stent insertion (two), percutaneous cholangiography with dilatation and stent placement (three), and conservative management (two). One patient died and the median inpatient stay following referral was 14 (range 7–78) days. Ten of 15 patients who had surgery before referral required a further biliary reconstruction. After median follow-up of 30 (range 3–60) months, four of nine patients with complex high injuries continue to have episodes of cholangitis and one patient has developed secondary biliary cirrhosis.

Conclusion Bile duct injury following laparoscopic cholecystectomy is a complex management problem and results in significant postoperative morbidity. Most patients referred after attempted repair require further reconstructive surgery, and patients with complex high injuries have a risk of long-term morbidity.

The universal implementation of laparoscopic cholecystectomy has brought significant advantages of shorter hospital stay, decreased postoperative morbidity and mortality rates, and a quicker return to normal activity for patients with gallstone disease[1–7]. Recent large collective reviews have shown that there is approximately twice the risk (0·6 *versus* 0·3 per cent) of bile duct injury following laparoscopic cholecystectomy compared with open cholecystectomy[8–10]. The mechanism and extent of biliary injury is different following laparoscopic cholecystectomy compared with the open procedure, with greater damage caused by the use of monopolar diathermy conducted along the bile duct, devascularization of the main bile duct during dissection, and a high frequency of inadvertent bile duct excision when the main bile duct is mistaken for the cystic duct and excised[8,11,12].

Early recognition of bile duct injury is essential to prevent major morbidity. The relative infrequency (approximately one in 200 cases) of major injury means that individual hospitals may not have the necessary skills and experience to carry out complex reconstructive procedures. A small but significant proportion of patients will have long-term problems with recurrent cholangitis and a risk of developing secondary biliary cirrhosis. This paper reports the management and outcome of bile duct injuries sustained at laparoscopic cholecystectomy in patients referred to a tertiary hepatobiliary and liver transplant centre.

Patients and methods

From 1991 to 1995, 27 patients were referred to this unit with major bile duct injuries sustained at laparoscopic cholecystectomy. Patients with minor bile leaks and those with cystic duct stump leaks were not included All 27 patients (18 women) had undergone elective cholecystectomy. The median age was 49 (range 25–67) years. Twenty patients were referred from hospitals within the West Midlands with a catchment population of approximately 5 5 million, and seven were referred from outside the region. At the time of laparoscopic cholecystectomy, surgery was described as uneventful in 14 patients and difficult because of adhesions in 13. Data on these patients were collected prospectively and referring hospital notes were reviewed wherever possible Details on the use of intraoperative cholangiography at laparoscopic cholecystectomy were not available for most patients. The case distribution over the 5-year period was five, eight, six, two and six cases per year from 1991 to 1995 respectively. All patients were followed up regularly with liver biochemistry. Patients with symptoms or cholestatic liver biochemistry underwent further imaging with ultrasonography, endoscopic retrograde cholangiography (ERC) or percutaneous cholangiography as required.

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Results

Presentation and management before referral

Initial clinical manifestations following bile duct injury were recorded at a median of 3 (range 0–700) days. The clinical presentation included abdominal pain ($n = 20$), fever ($n = 20$), jaundice ($n = 13$), subhepatic bile collection or 'biloma' ($n = 14$), bile-stained abdominal drainage ($n = 9$) and raised alkaline phosphatase level ($n = 17$). The median interval from laparoscopic cholecystectomy to referral was 26 (range 0–990) days. The median serum bilirubin concentration was 42 (range 10–836) mmol/l, and that of alkaline phosphatase was 893 (range 83–1690) units/l at the time of referral.

Fifteen patients underwent further surgery before referral: laparotomy and drainage ($n = 6$), bile duct suture ($n = 5$) and hepaticojejunostomy ($n = 4$). A further five patients underwent ultrasonographically-guided pigtail catheter drainage of subhepatic bile collections and three had a stent placed at ERC. Five patients were managed conservatively before referral. In six patients the injury was recognized at operation and all underwent surgical exploration: hepaticodochojejunostomy ($n = 3$), oversewing of divided right hepatic duct ($n = 1$), and end-to-end bile duct repair over a T tube ($n = 2$).

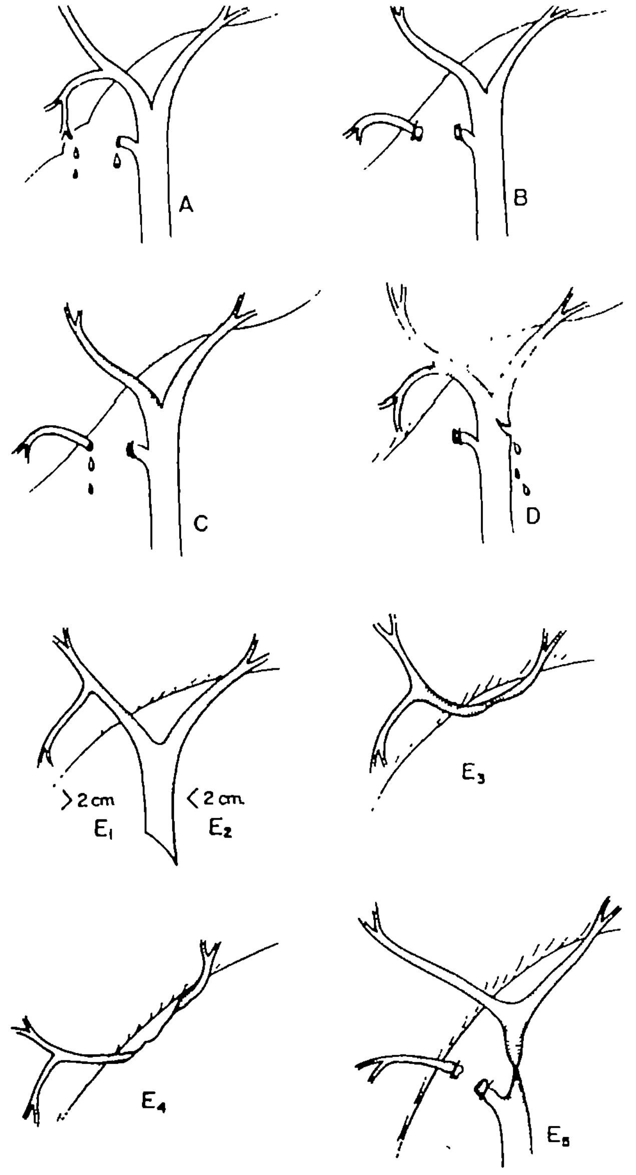

Fig. 1 Proposed classification of laparoscopic injuries to the biliary tract. The injuries Type A to E are illustrated. Type E injuries are subdivided according to the Bismuth classification. Type A injuries originate from small bile ducts that are entered in the liver bed or from the cystic duct. Type B and C injuries almost always involve aberrant right hepatic ducts. Type A, C, D, and some E injuries may cause bilomas or fistulas. Type B and other type E injuries occlude the biliary tree and bilomas do not occur. Reproduced from reference 8 with permission of the *Journal of the American College of Surgeons*

Type of injury

Bile duct injuries were classified according to the recently published classification proposed by Strasberg *et al.*[8] (*Fig. 1*), on the basis of ultrasonography ($n = 23$), ERC ($n = 21$), percutaneous cholangiography ($n = 12$) and surgical findings ($n = 20$). In 21 cases the common duct was divided and partially excised. Most referring surgeons at the time of referral felt that the injury was due to application of a clip to the common duct, rather than clipping and inadvertent excision of part of the common duct. The 27 bile duct injuries were classified as shown in *Table 1*. In addition two patients had an associated duodenal perforation.

Management after referral and outcome

Twenty patients underwent surgery, a majority (19) undergoing biliary enteric reconstruction: hepaticodochojejunostomy ($n = 15$), right hepaticodochojejunostomy ($n = 2$), separate right and left hepaticodochojejunostomies ($n = 1$), and hepaticodochojejunostomy and right accessory hepaticodochojejunostomy ($n = 1$); one patient underwent laparotomy with drainage. Approach to the biliary tree was made via a bilateral subcostal incision followed by careful dissection of the hilar area. In most instances the divided or clipped proximal duct was identified as a necrotic opening that was leaking bile, surrounded by indurated inflamed tissue related to the bile collection. The divided duct or ducts were dissected towards the hilum to obtain enough length to carry out a high anastomosis safely, and the necrotic cut or clipped end was excised to ensure viability. The biliary–enteric anastomosis to a proximal jejunal loop was carried out with 5/0 polydioxanone. Four of 19 patients undergoing reconstruction had at least one anastomosis carried out at a level above the bile duct confluence.

Table 1 Classification of bile duct injuries in the present series

		n
Type A	Leak from subvesical duct	1
Type B	Clipped and divided right segmental duct	0
Type C	Divided right segmental duct	3
Type D	Lateral injury common hepatic duct	1
Type E_1	Common hepatic duct division more than 2 cm from bifurcation	2
Type E_2	Common hepatic duct division less than 2 cm from bifurcation	11
Type E_3	Common duct division at bifurcation	5
Type E_4	Separate left and right hepatic duct strictures	3
Type E_5	Combined injury to main duct at bifurcation and right segmental bile duct	1

Two patients underwent ERC and stenting, two had ultrasonographically-guided pigtail catheter drainage of subhepatic bile collections and three underwent percutaneous transhepatic dilatation and stent placement (bile duct repair before referral). Two patients were managed conservatively after transfer. Of the 15 patients who underwent further surgery before referral, ten underwent biliary reconstruction, three were treated with percutaneous transhepatic dilatation and stenting (of whom two had had reconstruction and one bile duct suture previously), and two were managed conservatively.

The median inpatient stay after referral was 14 (range 7–78) days and median follow-up was 30 (range 3–60) months. Subsequent complications in these 27 patients included postoperative bile leak ($n=2$), restricture of bile duct ($n=2$), cholangitis ($n=4$), laparoscopic port-site hernia ($n=1$), intra-abdominal abscess ($n=1$), secondary biliary cirrhosis ($n=1$), pneumothorax ($n=1$), and abdominal bleed with sepsis/multiorgan failure and death ($n=1$).

The patient who died was a 64-year-old man referred 28 days after laparoscopic cholecystectomy (serum bilirubin 836 mmol/l, alkaline phosphatase 1521 units/l) in a moribund condition with a subhepatic bile collection, sepsis and renal failure. Before transfer he had undergone an ERC and sphincterotomy. Initial management included percutaneous drainage of the bile collection and intensive management of sepsis, malnutrition and renal failure. Three days after transfer he had a major abdominal and gastrointestinal bleed and underwent a laparotomy at which a posterior perforation of the second part of the duodenum was found (related to the endoscopic sphincterotomy), in addition to a large defect in the mid bile duct (type E_2 injury) and an indurated inflamed subhepatic abscess cavity. Because of the extensive local and systemic sepsis, a reconstructive procedure could not be carried out. The duodenal defect was repaired, a T tube was placed across the bile duct defect, and external drainage achieved. The patient died 10 days later from worsening sepsis and multiorgan failure.

At present 20 patients are asymptomatic and well, and two others have upper abdominal pain with normal liver biochemistry. Of the nine patients with complex E_3, E_4 and E_5 injuries involving the segmental ducts, four have had recurring cholangitis and one has developed secondary biliary cirrhosis.

Discussion

The incidence of bile duct injury following laparoscopic cholecystectomy has been shown to be higher than that observed after open cholecystectomy (0·6 *versus* 0·3 per cent)[8–10]. Several factors may contribute to this: misidentification of the common, right or aberrant right duct as the cystic duct followed by its excision, division or occlusion; excessive traction on the gallbladder resulting in tenting of the main bile duct; devascularization or thermal injury to the common duct; the experience of the operating surgeon and the learning curve effect; local operative factors, including inflammation, fat, haemorrhage, too deep dissection of the gallbladder bed; and problems related to equipment such as the use of laser, or clip failure[8,11]. Because of differences in the mechanism and extent of injury following laparoscopic cholecystectomy, the existing Bismuth classification[13] for bile duct injuries and strictures does not cover all possibilities. In this study bile duct injuries after laparoscopic cholecystectomy were classified according to the system proposed by Strasberg *et al.*[8] (*Fig. 1*). The even distribution of referrals over the 5-year period suggests that bile duct injury after laparoscopic cholecystectomy continues to be a major problem, and not one merely related to the introduction of a new surgical technique.

Bile duct injury following laparoscopic cholecystectomy occurs approximately once in every 200 cases, an incidence too low for any individual surgeon to develop the skills and experience required to treat these difficult problems. In addition, the associated interventional radiological and endoscopic skills required to achieve stenting or drainage are not available in most referring hospitals. These are strong arguments in favour of management of such complications at specialist tertiary centres where facilities and multidisciplinary teams exist to manage them.

The role of intraoperative cholangiography to help prevent bile duct injury is unclear[14–16]. Since most injuries occur as a result of inadvertent clipping and division of the common duct that has been mistaken for the cystic duct, the injury will have occurred before the cholangiography catheter is inserted. However, failure to demonstrate the common and intrahepatic ducts at cholangiography would serve to alert the surgeon that the common duct has been cannulated, and would prevent further compounding of the injury by inadvertent resection of part of the common duct. This particular injury and its variant are the most commonly reported major bile duct injuries following laparoscopic cholecystectomy[8,11,17]. The authors were unable to obtain information on the use of intraoperative cholangiography at laparoscopic cholecystectomy in a majority of patients in this series.

Early recognition of bile duct injury is crucial in further management. The only patient who died was referred 4 weeks after laparoscopic cholecystectomy, with an inadequately drained subhepatic bile collection, a duodenal fistula with established systemic sepsis and multiorgan failure. The possibility of biliary injury should be considered in patients who undergo a difficult or prolonged laparoscopic dissection of Calot's triangle, followed by the development of pain, fever and altered liver biochemistry, and in those with bile observed in subhepatic drains. Halevy *et al.*[18] suggested that abnormal postoperative transaminase levels were not of any predictive value. However, this was in a small study of only 67 patients undergoing laparoscopic cholecystectomy. Most injuries are not recognized at laparoscopic cholecystectomy, although most patients do have symptoms and signs early after operation. Only a small proportion of injuries was recognized at operation (six of 27); in all of these patients laparoscopic cholecystectomy was converted to an open procedure and surgical repair was carried out in five (bile duct suture in two and hepaticodochojejunostomy in three), with oversewing of a divided right accessory duct in one.

There was a significant period of delay between observation of the first symptoms suggesting a biliary complication (median 3 days) to eventual referral to a hepatobiliary centre for definitive management (median 26 days). The extent of bile duct injury was not defined in most patients by the time they were referred. Most surgeons delayed the request for ERC and, even when this was carried out, the commonest interpretation was of a clip occluding the bile duct, rather than clipping

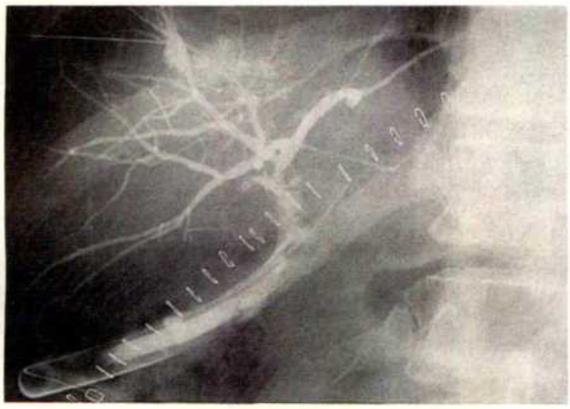

Fig. 2 Tubogram via a subhepatic abdominal drain showing communication with the biliary tree in a patient with a high E_2 injury, who underwent an additional laparotomy before referral

followed by division and partial excision of the common duct. Also, by the time patients were transferred to this unit, 15 of them had already undergone a further surgical procedure in an attempt to diagnose the site of leakage (*Fig. 2*). Two-thirds (ten of 15) of these reoperated patients needed definitive surgery following referral, and three others required further percutaneous intervention for early stricture after repair before referral. We feel that patients with a suspected bile duct injury should be referred immediately to a specialist hepatobiliary unit where the necessary infrastructure, experience and skills exist, minimizing the risk of long-term complications.

The distribution of cases with a large proportion of high ductal injuries (20 of 27 injuries involving the confluence or within 2 cm of the confluence) suggests that the more complex injuries are being referred to tertiary units, albeit with a significant delay. Similar findings have been reported by other hepatobiliary centres, suggesting that less severe injuries may be being treated at referring units. Biliary reconstruction in these cases almost always involves a major dissection into the hilar area, often to ducts as small as 2–3 mm in size, occasionally with more than one anastomosis, in the presence of severe inflammation due to subhepatic bile collections and systemic sepsis. Conventional management of post-traumatic bile duct stricture usually advocates surgery once the bile duct has strictured down and the proximal ducts have dilated significantly thereby facilitating reconstructive surgery. After laparoscopic cholecystectomy, most patients present either with a total biliary fistula (*Fig. 2*), with its associated problems of electrolyte and fluid loss, malabsorption, sepsis and the psychological problems of external bile leakage, or with localized or generalized biliary peritonitis, where it is often difficult to achieve effective drainage. A majority of these patients underwent reconstructive surgery fairly early after referral, although this does involve operating on non-dilated ducts high at the level of the hilar bifurcation. Although the follow-up period is relatively short (median 30 months), only two patients developed postoperative leaks which settled spontaneously, and there were two postoperative strictures, one in a patient with the previously mentioned postoperative leak. Both patients with strictures were managed by percutaneous dilatation.

Patients with injuries involving the segmental ducts (E_3 and E_4 in the Strasberg classification) have continuing long-term morbidity with a higher incidence of recurring cholangitis despite careful surveillance for restricturing and percutaneous dilatation of high segmental strictures. One patient already has secondary biliary cirrhosis, and over the course of time this will develop in others as well. Several patients have already undergone liver transplantation for secondary cirrhosis following bile duct injury at open cholecystectomy carried out years earlier, and it is very likely that a small proportion of bile duct injuries after laparoscopic cholecystectomy may be considered for transplantation in the future, thereby adding significantly to long-term morbidity.

In conclusion, bile duct injury following laparoscopic cholecystectomy is an infrequent but serious complication that may result in significant long-term morbidity. Biliary injury should be suspected in patients following a difficult laparoscopic procedure or in those who are unwell with abdominal pain or fever, with bile observed in subhepatic drains, or in those with abnormal postoperative liver biochemistry. Abdominal ultrasonography followed by early ERC are the investigations of choice. If a subhepatic or abdominal bile collection is seen, percutaneous pigtail catheter drainage should be achieved. Early transfer to specialized tertiary centres with additional surgical, radiological and endoscopic skills available, without resorting to further surgical exploration is recommended, so that surgical repair if required can be carried out and morbidity decreased.

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Surgical workshop

Reinsertion of the distal common bile duct into the resection cavity during duodenum-preserving resection of the head of the pancreas for chronic pancreatitis

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Chronic pancreatitis with predominant involvement of the head of the pancreas frequently generates distal common bile duct (CBD) stenosis[1]. Various therapeutic modalities have been proposed to control pancreatitis-related CBD stricture.

Duodenum-preserving resection of the head of the pancreas, which has been shown to be a safe and effective option in the treatment of chronic pancreatitis, also provides permanent control of CBD stenosis by decompression of the bile duct in its intrapancreatic course[2,3]. However, in some patients the wall of the CBD is destroyed by the chronic inflammatory process and ductal continuity cannot be preserved during decompression of the CBD. In these instances restitution of bile passage is achieved by bilioenteric anastomosis to bypass the intrapancreatic course of the CBD[1].

In combination with duodenum-preserving resection of the head of the pancreas as described by Beger and Büchler[2] or Frey and Amikura[4], a technique of reinsertion of the distal CBD into the resection cavity of the pancreatic head is described to avoid this additional bilioenteric anastomosis.

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Surgical technique

In duodenum-preserving resection of the head of the pancreas decompression of the distal CBD in its intrapancreatic course is sometimes necessary. To identify the CBD properly and to avoid injury a metal probe is passed transpapillary through a proximal

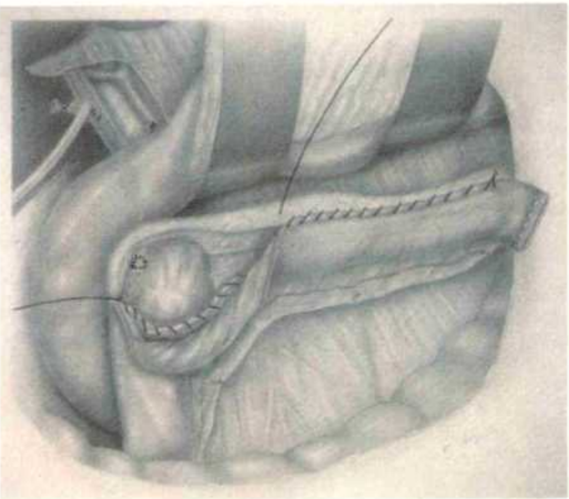

Fig. 1 Duodenum-preserving resection of the head of the pancreas as described by Frey, with reinsertion of the common bile duct into the resection cavity

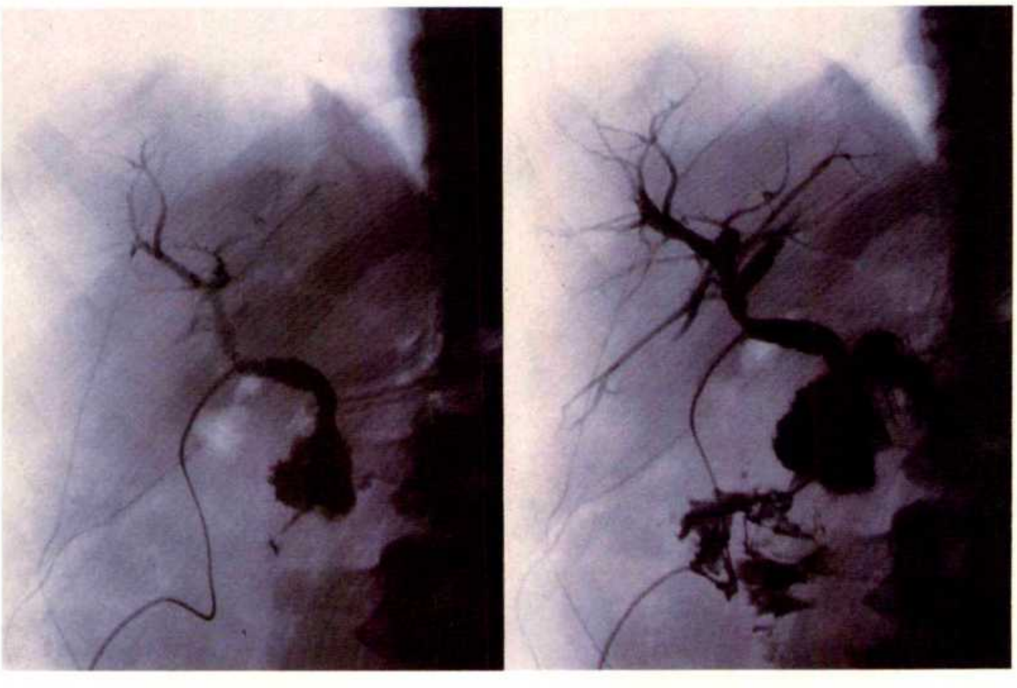

Fig. 2 T tube cholangiogram 7 days after duodenum-preserving resection of the head of the pancreas with bile drainage into the resection cavity. Printed with permission of the Demeter-Verlag, Balingen, Germany

choledochotomy. If the CBD in its intrapancreatic course is narrowed, decompression may result in injury of the distal segment of the CBD.

The inflamed intrapancreatic distal bile duct segment is resected. The proximal, but still intrapancreatic, CBD is reinserted into the resection cavity of the pancreatic head with circular fixation to the retroduodenopancreatic plate using a single-stitch technique with a 5/0 absorbent monofilament suture (*Fig. 1*). Thus the bile pours into the resection cavity of the pancreatic head and mingles with pancreatic secretion to be drained by a side-to-side pancreatojejunostomy (*Fig. 2*).

Through the proximal choledochotomy a T tube is placed into the CBD to drain biliary secretion. This T tube is removed after 10 days.

Discussion

Duodenum-preserving resection of the head of the pancreas represents a therapeutic option that maintains the anatomical situation by restoring the normal bilioduodenal passage. Thus, diagnostic and interventional endoscopy remains feasible. However, in some patients continuity of the distal CBD cannot be preserved.

In a series of 105 consecutive patients with chronic pancreatitis who underwent duodenum-preserving resection of the head of the pancreas, 52 patients presented with distal CBD stenosis. In 13 patients the continuity of the CBD could not be preserved. Until 1993 bile passage was restored by an additional suprapancreatic bilioenteric anastomosis in six patients. Since 1993 reinsertion of the CBD was performed in seven patients as described above (Beger's and Frey's operation in three and four patients respectively). During a median follow-up of 24 months no patient with reinsertion of the CBD into the pancreatic resection cavity suffered recurrent pain, cholangitis or recurrent biliary obstruction.

In cases of discontinuity of the intrapancreatic course of the CBD, reinsertion of the distal bile duct into the resection cavity represents a safe, quick and effective technique to restore biliary drainage. A separate anastomosis between the CBD and the interposed jejunal loop as described by other authors[2] is not required.

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Prediction of postoperative decompensated liver function by technetium-99m galactosyl-human serum albumin liver scintigraphy in patients with hepatocellular carcinoma complicating chronic liver disease

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Background Preoperative technetium-99m galactosyl-human serum albumin (Tc-GSA) liver scintigraphy may predict postoperative decompensated liver function and its value has been investigated in patients having resection of hepatocellular carcinoma (HCC).

Methods Hepatic uptake ratio of Tc-GSA (LHL15) was measured before operation in 30 patients. Postoperative complications were analysed retrospectively and compared with LHL15 values and other indicators evaluating hepatic function.

Results The LHL15 of 22 patients without complications was 0·91 or more, compared with 0·90 or less in the eight patients who had complications. Multifactorial analyses showed that LHL15 and Child–Pugh grade significantly predicted postoperative complications ($P < 0.0001$ and $P = 0.0111$ respectively). LHL15 was a significant predictor of complications in patients with Child–Pugh grade B disease ($n = 15$, $P = 0.0011$).

Conclusion LHL15 was a reliable preoperative indicator of the risk of major postoperative complications in patients who had resection for HCC.

The best chance of survival for patients with primary as well as secondary liver tumours is surgical resection, although several non-surgical therapeutic modalities have been developed[1,2]. However, the incidence of postoperative morbidity and death following resection of hepatocellular carcinoma (HCC) is higher than that after resection for colorectal liver metastasis[3] because of the poor hepatic functional reserve resulting from co-existing chronic liver disease[2,4–6]. Therefore, the appropriate selection of patients for hepatic resection, using a reliable predictor of operative risk, is mandatory in the management of patients with HCC[4].

Recent studies have shown that liver scintigraphy using a newly developed radiopharmaceutical, technetium-99m galactosyl-human serum albumin (Tc-GSA), which specifically binds to the asialoglycoprotein receptors on the hepatocellular membrane[7], is a novel method for assessing hepatic function[8]. Although the value of Tc-GSA has been shown in the evaluation of hepatocellular function in patients with chronic liver disease[9], it is not known whether preoperative Tc-GSA scintigraphy can predict postoperative complications based on poor liver function after hepatectomy for HCC in patients with chronic liver disease. The value of preoperative assessment by Tc-GSA liver scintigraphy for predicting postoperative complications in patients with HCC and chronic liver disease was therefore studied.

Patients and methods

Seventy-two patients (median age 64·1 (range 50–76) years) with HCC co-existing with liver cirrhosis or chronic hepatitis were admitted between May 1992 and June 1995. Thirty of these patients (median age 64·0 (range 54–75) years) were diagnosed as resectable by assessment with the clinical criteria defined by Makuuchi *et al.*[10] and Noguchi *et al*[4], which consist of the grade of ascites, serum bilirubin and albumin levels, indocyanine green (ICG) clearance test and prothrombin test. All 30 patients underwent hepatic resection. The diagnosis of HCC and chronic liver disease in the 30 patients was confirmed histologically. The type of hepatectomy performed was classified as partial resection, subsegmentectomy, segmentectomy or lobectomy. During parenchymal resection, haemostasis was accomplished with electric cautery and ligation but without hilar inflow occlusion.

All 30 patients underwent Tc-GSA liver scintigraphy as described by Kudo *et al.*[9,11]. Some 3 mg Tc-GSA (185 MBq) (Nihon Medi-Physics, Nishinomiya, Japan) was administered as a bolus intravenous injection. Dynamic imaging was performed with the patient in the supine position under a large field of view gamma camera equipped with a low-energy all-purpose parallel-hole collimator centered on the liver and then on the precordium, using a General Electric Starcam 3000X-RT (General Electric, Milwaukee, Wisconsin, USA). Computer acquisition of the gamma camera data on centered spots was started just before the injection of Tc-GSA and stopped at 20 min after the injection. Digital images (128 × 128 pixels) were acquired in byte mode at a rate of 15 s per frame. Static images of the anterior abdominal view were obtained at 5, 10, 15 and 20 min after the injection. Time–activity curves for both the heart and the liver were generated from regions of interest (ROIs) for the liver and precordium. The hepatic uptake ratio of Tc-GSA (LHL15) was calculated by dividing the radioactivity of the liver ROIs by that of the liver plus heart ROIs at 15 min after the injection, as described by Kudo *et al*[11]. Hepatectomy was carried out in all 30 patients within 1 or 2 weeks after Tc-GSA scintigraphy.

The plasma retention rate of ICG 15 min after the injection (ICG R15) was measured by administering an intravenous injection at a dose of 0·5 mg ICG per kg body-weight, as described previously[12–14].

Univariate and multivariate analyses were employed to investigate whether LHL15 is a useful indicator for assessing

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postoperative poor liver function. All statistical analyses, including Mann–Whitney *U* test, χ^2 test and multifactorial test, were performed using the computer software package Statview IV (Abacus Concepts, Berkeley, California, USA). A difference was considered to be significant when the *P* value was less than 0·05.

Results

Eight of the 30 patients suffered major postoperative complications and the overall postoperative morbidity rate was 27 per cent, whereas the other 22 patients had an uneventful postoperative course. Three patients had postoperative hepatic failure, three had hyperbilirubinaemia (greater than 5·0 mg/dl), one had hyperbilirubinaemia with a large amount of ascites and one had hyperbilirubinaemia with intra-abdominal infection. Three patients died within 30 days after operation. The other 27 patients were alive as of October 1995, and the follow-up of these patients ranged from 4 to 36 (mean 16·7) months.

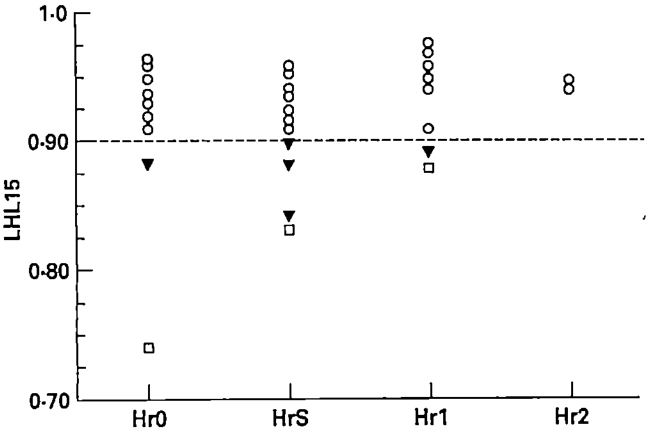

Fig. 1 LHL15 level classified by type of hepatectomy in patients who had an uneventful recovery (○), postoperative complications (▼) or died in hospital (□). Hr0, partial resection; HrS, subsegmentectomy; Hr1, segmentectomy; Hr2, lobectomy. LHL15 values of all patients with an uneventful course were 0·91 or more, regardless of the type of hepatectomy

A large intraoperative blood loss (3120 ml) was observed in a patient who died from a major postoperative complication. However, seven other patients with postoperative complications lost relatively small volumes of blood (mean 1148 ml). LHL15 values in all eight patients with major complications were less than or equal to 0·90 (*Fig. 1*). In contrast, the LHL15 values of the 22 patients with an uneventful course were 0·91 or more. Of these 22 patients, six with Child–Pugh grade B disease, whose LHL15 values were more than or equal to 0·91 and whose intraoperative blood loss was more than 1500 ml, had no major postoperative complications.

Preoperative assessment of hepatic function and operative factors were compared univariately with the postoperative morbidity (*Table 1*). Of the preoperative assessments, serum bilirubin levels were significantly lower and LHL15 levels were significantly higher in patients who had an uneventful recovery than in those with postoperative complications ($P = 0·04$ and $P < 0·0001$ respectively). The type of operation, duration of the operation, amount of blood loss and tumour diameter were not significantly different between the groups of patients with and without postoperative complications.

Multiple regression analysis showed that LHL15 and Child–Pugh grade significantly predicted postoperative complications ($R^2 = 0·580$; *Table 2*). When the postoperative complications were also multifactorially analysed in the 15 patients classified as Child–Pugh grade

Table 1 Comparison of preoperative hepatic function and operative factors between patients with postoperative complications and those with an uneventful recovery

	Patients with postoperative complications ($n = 8$)	Patients with uneventful recovery ($n = 22$)	*P*
Preoperative assessment of liver functional reserve			
Prothrombin test (%)*	79·1(4·4)	86·5(4·6)	0 51§
Total serum bilirubin (mg/dl)*	1·0(0·1)	0·8(0·1)	0·04§
Albumin (g/dl)*	3·5(0·1)	3·6(0·1)	0·60§
LHL15*	0·85(0·02)	0·94(0·01)	<0·0001§
ICG R15 (%)*	18·2(2·4)	16·3(1·3)	0·64§
Child–Pugh grade*	6·3(0·3)	6·2(0·2)	0·88§
Patients with liver cirrhosis†	8 (100)	14 (64)	0·13¶
Operative factors			
Duration of operation (min)*	421·6(67·3)	457·4(47·2)	0·55§
Blood loss (ml)*	1395·1(282·3)	1138·8(141·9)	0·32§
Maximum diameter of tumour (mm)*	31·9(2·9)	32·0(2·4)	0·83§
Clinical stage‡			
I	1	6	0·72¶
II	7	16	
Type of operation			
Partial resection	2	7	0·72¶
Subsegmentectomy	4	7	
Segmentectomy	2	6	
Lobectomy	0	2	

*Values are mean(s.e.m.). †Values in parentheses are percentages. ‡Current American Joint Committee on Cancer staging system for hepatocellular carcinoma. LHL15, hepatic uptake ratio of technetium-99m galactosyl-human serum albumin; ICG R15, indocyanine green plasma retention rate after 15 min. §Mann–Whitney *U* test; ¶χ^2 test

Table 2 Multiple regression analysis for postoperative complications in patients undergoing hepatectomy

	Patients undergoing hepatectomy ($n = 30$)		Patients with Child–Pugh grade B disease ($n = 15$)	
	Standard coefficient	P	Standard coefficient	P
Child–Pugh grade	−0·333	0·0111	—	—
LHL15	−1·040	<0·0001	−1·300	0·0011
ICG R15	−0·148	0·2851	−0·260	0·1856
Total bilirubin	−0·207	0·2594	−0·168	0·4891
Clinical stage*	−0·159	0·4013	−0·606	0·1190
Operation	0·038	0·8404	0·733	0·0897
Duration of operation	0·061	0·6594	−0·527	0·0642
Amount of blood loss	0·077	0·5853	−0·132	0·5152

*Current American Joint Committee on Cancer staging system for hepatocellular carcinoma. LHL15, hepatic uptake ratio of technetium-99m galactosyl-human serum albumin; ICG R15, indocyanine green plasma retention rate after 15 min

B, LHL15 value was shown to be the only significant independent variable ($R^2 = 0{\cdot}732$).

Discussion

The present study demonstrated that the LHL15 level predicted postoperative poor liver function in patients with HCC accompanying chronic liver disease, and suggested that Tc-GSA liver scintigraphy is a reliable modality for evaluating hepatic functional reserve in these patients.

Tc-GSA, which is one of the asialoglycoproteins, specifically binds to asialoglycoprotein receptors existing only on the hepatocellular membrane, with minimal interstitial distribution, and is a unique agent for evaluating hepatocellular function since the binding reaction rate is sensitive to alterations in hepatic blood flow and receptor biochemistry[15,16]. The LHL15 level, which is an indicator of hepatic uptake of Tc-GSA for assessing the biochemical reaction between the receptor and the ligand in the liver, is reported to be a reliable method for evaluating hepatic function in patients with chronic liver disease and significantly correlates with conventional methods for evaluating hepatic functional reserve[9,17]. However, it has yet to be clarified whether the LHL15 level is a more accurate predictor of the postoperative course than any other conventional hepatic assessment.

Although the indications for hepatectomy in the present study were comprehensively determined by the criteria of Makuuchi *et al.*[10] and Noguchi *et al.*[4], which include conventional assessments that are thought to estimate preoperative hepatic functional reserve, these criteria could not satisfactorily assess the hepatic functional reserve. Indeed, eight patients had major postoperative complications and there were three deaths in this series. The LHL15 levels of the eight patients with complications were less than or equal to 0·90 (*Fig. 1*), while patients in whom the LHL15 level was 0·91 or more did not have any major postoperative morbidity. The ICG R15 level, which has been reported as a predictor for postoperative complications[12], was not significantly different between patients with and without postoperative morbidity (*Table 1*). In addition, the intraoperative blood loss in the eight patients was not significantly different from that in the 22 patients with an uneventful course. Indeed, six patients with Child–Pugh grade B disease and an intraoperative blood loss of more than 1500 ml had an uneventful recovery after operation and had LHL15 levels of 0·91 or more before surgery. Therefore, it is suggested that LHL15 is a reliable preoperative indicator of the risk of postoperative complications regardless of the intraoperative blood loss, as well as the type of operation.

Multiple regression analysis showed that the LHL15 level and the Child–Pugh grade significantly indicate the risk of major postoperative complications, and that the LHL15 level predicts postoperative complications based on poor liver function in patients with Child–Pugh grade B disease (*Table 2*). The findings suggest that the LHL15 level is a useful preoperative indicator of hepatic functional reserve in patients with Child–Pugh grade B disease, in whom a reliable preoperative assessment indicating the risk of the major postoperative complications is exceedingly important.

Although the ICG clearance test is a widely accepted method of assessing hepatic functional reserve[13,14], the ICG R15 level is mainly dependent on hepatic blood flow and intrahepatic–extrahepatic shunt[18]. Moreover, ICG R15 has been shown to be an unreliable marker for hepatic functional reserve in jaundiced patients because the ICG receptor of hepatocytes also has an affinity for bilirubin[19]. In contrast, it has been shown that Tc-GSA binding to asialoglycoprotein receptors is not interfered with by high serum bilirubin levels since the asialoglycoprotein receptor does not bind to bilirubin[20–22]. Indeed, it has been reported that Tc-GSA liver scintigraphy is also effective for the assessment of hepatocellular function in the presence of hyperbilirubinaemia[8,23]. In addition, the LHL15 value was shown to reflect hepatocellular function even in the presence of a large portacaval shunt, such as in patients with idiopathic portal hypertension in whom the values derived from conventional liver function tests are demonstrated to be much lower than the actual liver functional reserve[9]. These reports support the suggestion that Tc-GSA liver scintigraphy could be widely useful for selecting patients for liver resection.

A larger study may be needed to confirm the value of Tc-GSA liver scintigraphy, but the present results suggest that the LHL15 level is a reliable preoperative indicator of the risk of major postoperative complications in patients with HCC and co-existing liver cirrhosis or chronic hepatitis.

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Analysis of renal artery geometry may assist in the design of new stents for endovascular aortic aneurysm repair

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Background Endovascular repair of infrarenal aortic aneurysms is a feasible technique, but up to 30 per cent of patients may be excluded on the basis of a short proximal aortic neck.

Methods A dissection study was performed on 65 cadavers to measure the distance between the superior mesenteric and renal artery ostia, and to document the points of origin of the renal arteries.

Results The interostial distance did not differ significantly between aneurysmal and non-aneurysmal aortas (P = 0·90 for the left renal artery; P = 0·72 for the right). The median distance was 0·7 cm. The renal arteries originated between 2 and 4 o'clock on the left and between 9 and 10 o'clock on the right.

Conclusion The relative consistency of the anatomy in this region may allow the development of a new stent which would increase the number of patients suitable for endovascular repair.

Abdominal aortic aneurysm (AAA) is a life-threatening condition affecting up to 5 per cent of men over the age of 65 years[1,2]. The pioneering work of Parodi and others[3] has established a new technique of endovascular repair which avoids the need for an abdominal incision or for cross-clamping of the aorta. Up to 40 per cent of patients who suffer from AAA have significant coronary artery disease with reduced cardiac reserve[4,5]. Such patients may benefit from avoiding the haemodynamic changes of aortic cross-clamping and blood loss.

Although endovascular repair has potential advantages over open aneurysm repair, the number of suitable patients is limited by the geometry of the AAA. In particular, a short proximal aortic neck, a highly angulated aneurysm or very tortuous iliac arteries may prevent successful deployment of an endovascular device. The proximal stent needs a relatively undiseased and non-aneurysmal neck of infrarenal aorta about 2 cm or more in length for implantation, although some devices have been deployed in a neck as short as 1 cm[6]. Patients with small aneurysms may have a sufficiently long infrarenal aortic neck, but nearly 30 per cent of those with large or symptomatic aneurysms will be unsuitable for endovascular repair because of a short proximal aortic neck[7].

Close examination of the region of the aorta bounded above by the superior mesenteric artery and below by the renal arteries has been performed previously with a view to improving the success of renal artery angiography and as an anatomical exercise[8–15].

The aims of this study were to measure the geometry at the level of the renal arteries and to document the points of origin of the renal arteries around the aortic wall. This information was analysed with a view to designing new stents for the proximal part of aortic stent grafts.

Materials and methods

After ethics committee approval, 65 human cadavers (median age 83 (range 62–104) years; 36 men and 29 women), preserved in identical fashion, were dissected to expose the abdominal aorta[16]. The maximum infrarenal aortic diameter was measured three times using callipers. The angle made by the neck of an aneurysm with the aneurysm itself was measured with a goniometer in sagittal and coronal planes. In cadavers with an AAA, the length of the proximal neck was measured. The aorta was transected immediately below the lower renal artery and viewed from its inferior end. A 360° protractor marked with concentric circles and divided into sectors of 10° was positioned flush with the cut end of the aorta such that the aorta was centred on it and 0° was in the midline anteriorly. The positions of the renal artery ostia were recorded in degrees; the ostial edge closest to the sagittal plane was used as the point of measurement.

The aorta was opened posteriorly in the midline. The shortest distance between the inferior edge of the ostium of the superior mesenteric artery and the superior edge of each renal artery ostium (the interostial distance) was measured three times using callipers.

Histographic analysis of the interostial distance did not suggest a normal distribution of measurements. Therefore, comparisons between aneurysmal and non-aneurysmal aortas were performed using the Mann–Whitney U test. Repeated measurements were analysed for the within-subject standard deviation and repeatability[17].

Results

Maximum infrarenal aortic diameter

Eleven (17 per cent) of the 65 cadavers had an AAA (maximum aortic diameter greater than or equal to 5 cm). The median aneurysm diameter was 5·3 (interquartile range (i.q.r.) 5·0–5·5) cm. None of the aneurysms was seen to extend into the common iliac arteries.

Angle of the proximal neck

The median angle made by the proximal neck with the body of the aneurysm was 30 (i.q.r. 0–45)° in the sagittal plane and 40 (i.q.r. 5–60)° in the coronal plane.

Length of the proximal neck

The median length of the proximal neck was 0·9 (i.q.r. 0·3–1·9) cm.

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Table 1 Interostial distance in aneurysmal and non-aneurysmal cadaveric aortas

	Non-aneurysmal ($n = 54$)	Aneurysmal ($n = 11$)
SMA to left renal artery (cm)	0·7 (0·3–1·1)	0·7 (0·3–1·0)
SMA to right renal artery (cm)	0·7 (0·0–1·0)	0·8 (0·3–1·0)

Values are median (interquartile range). SMA, superior mesenteric artery

Interostial distance

The interostial distance is shown in *Table 1*. Comparison of these data shows no statistically significant difference between the aneurysmal and non-aneurysmal aortas (Z statistic = −0·12, P = 0·90 for the left renal artery; Z statistic = −0·37, P = 0·72 for the right renal artery). Although the median values are about 0·7 cm, in 12 aortas (18 per cent) both interostial distances were over 1 cm with maximum values in one cadaver of 2·6 cm on the left and 2·4 cm on the right. The within-subject standard deviation of repeated measurements was 0·04 cm and the repeatability 0·1 cm.

Origin of the renal arteries

All left renal arteries arose between 60 and 120°, and all right renal arteries between 270 and 300° (*Fig. 1*). Accessory renal arteries were present in 13 cadavers (20 per cent), two of which had an AAA, and were more common on the right where they tended to arise from the anterior wall of the aorta. The accessory arteries were single and unilateral in all cases.

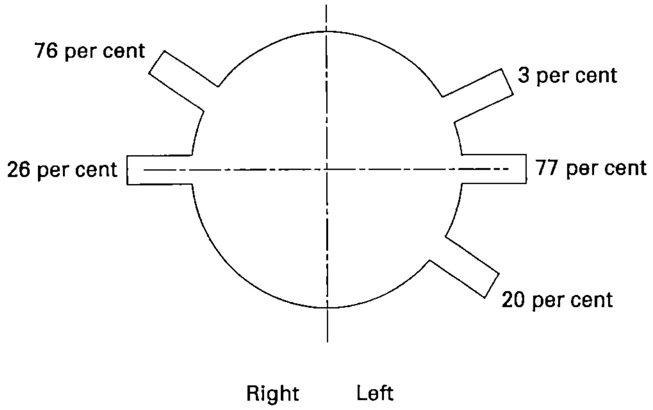

Fig. 1 Cross-section of the aorta showing the relative positions of the origins of the renal arteries

Discussion

Thirty per cent of patients who are otherwise suitable for endovascular aneurysm repair will be excluded by virtue of a short proximal aortic neck. To overcome this limitation a change in the design of the proximal stent could be made based on the anatomy of the aorta at the level of the renal arteries.

The sample population examined had a median age 15–20 years higher than that of the typical patient having AAA repair. The male to female ratio was also more even than in the usual patient sample where there is a preponderance of men. These deficiencies were determined by the source of the study group. Notwithstanding these differences, there is considerable agreement between the results of this study and measurements of aortic geometry made in patients by computed tomography[6,18].

The interostial distance did not differ significantly between specimens with and without an AAA and in 19 per cent of cadavers was longer than the neck length of some patients already treated by endovascular repair. The points of origin of the renal arteries were remarkably consistent allowing sectors of the aortic circumference between them to be considered 'safe'. Therefore, it is conceivable that patients with a very short proximal neck could be offered endovascular repair using a new stent which would be fixed partly above and partly below the renal ostia, the two segments being connected by longitudinal struts running in safe areas outside the points of origin of the renal arteries.

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Short note

Major vascular injury during laparoscopy

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Injury to the major abdominal vessels is an uncommon complication of laparoscopy[1]. Five cases treated over the past 6 years are presented.

Case reports

In every case surgery was started by insufflation of carbon dioxide through a Veress needle inserted subumbilically in the direction of the pelvis followed by the blind introduction of a 10-mm trocar along the same track.

Patient 1

A 31-year-old woman developed hypotension and tachycardia in the recovery room after routine diagnostic laparoscopy. At laparotomy a large retroperitoneal haematoma was evident. A right common iliac artery laceration was repaired. Seven units of blood were transfused.

Patient 2

A 27-year-old woman having a laparoscopic cholecystectomy suffered complete transection of the right common iliac artery and laceration of both anterior and posterior walls of the inferior vena cava. The venous lacerations were sutured after mobilization of the cut ends of the right common iliac artery. The artery was then repaired end to end. Four units of blood were given. This patient developed a right iliofemoral vein thrombosis, but following anticoagulation there was no leg oedema.

Patient 3

A 29-year-old woman undergoing diagnostic laparoscopy for infertility developed hypotension and tachycardia immediately after introduction of the laparoscope. A small amount of blood in the pelvis and a retroperitoneal haematoma were noted. Through a Pfannenstiel incision, prolonged attempts were made at local control of a small bleeding laceration in the posterior parietal peritoneum. The patient remained haemodynamically unstable. Some 50 min after laparotomy, a vascular surgeon was summoned. A long midline incision was immediately made. Lacerations of the right iliac artery and vein were encountered. Despite immediate local control of the artery and vein, bleeding continued from the presacral plexus. Despite transfusion of 22 units of blood, cardiac arrest ensued from which the patient could not be revived.

Patient 4

In an 18-year-old woman having laparoscopic oöphorectomy, tachycardia and intraperitoneal bleeding were noted immediately after insertion of the laparoscope. Temporary haemostasis was obtained by direct pressure through a midline lower abdominal incision while blood was obtained and the vascular surgical team called. The left common iliac vein was ligated on either side of a through and through laceration. Eight units of blood were transfused. No oedema of the leg was seen at follow-up.

Patient 5

A 12-year-old girl undergoing laparoscopic ovarian surgery was seen to have retroperitoneal bleeding soon after the procedure was started. Through a midline laparotomy, haemorrhage was controlled immediately with vascular clamps. Lateral repair of a small right common iliac vein tear was performed. No blood was required.

Discussion

In every case the vascular injury occurred during blind introduction of a trocar towards the pelvis through an infraumbilical incision. Open trocar placement reduces the incidence of such injuries[2,3].

Recognition of the injury was frequently delayed. The patients were mostly fit and young, maintaining their blood pressure for some time, even during major haemorrhage. The operating team, being prepared for a minor procedure, tended to make an inadequate laparotomy incision even when haemorrhage was recognized, with fatal results in one case.

From this experience, and the reported experience of others[4,5], the authors consider that the following points should be emphasized:

1. Both the surgeon and the patient should be prepared for this uncommon complication. Blood bank facilities and adequate anaesthetic and surgical back-up should be available.
2. It would seem advisable to introduce the first trocar under vision. This is the most likely single measure to prevent vascular injuries.
3. An adequate incision is essential for vascular control and repair.
4. Initially, minimal haemostatic measures should be used, allowing for volume replacement, preparation of blood for transfusion and experienced help to arrive.
5. Lacerations of the iliac vein may be ligated. Arterial injuries can usually be treated by debridement and primary suture. Combined injuries may be treated by dividing the overlying artery, ligating the lacerated vein and then repairing the artery.

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Short note

Improving the preoperative assessment of varicose veins

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Recurrence rates of between 6 and 60 per cent[1] following surgery for varicose veins have largely been attributed to inadequate surgery[2]. The contribution of inaccurate preoperative assessment (resulting in inappropriate surgery) to the development of recurrence has not been evaluated.

Traditionally, surgery for varicose veins has been based on clinical examination with the aid of a tourniquet[3]. In recent years, the accuracy of this technique has been improved by the additional use of hand-held Doppler ultrasonography[4]. On specialized units, colour flow duplex scanning has become the ‘gold standard’ varicose vein assessment[5]. This study compared traditional clinical examination, with and without the use of Doppler ultrasonography, with colour flow duplex scanning in the preoperative assessment of varicose veins.

Patients and methods

Seventy-one limbs in 49 patients (34 women, 15 men) with primary varicose veins were included in the study. The median age was 37 (range 18–66) years. Each patient was examined by three surgeons using different techniques. Surgeon A used the traditional technique of clinical examination with a tourniquet. In addition to clinical examination with a tourniquet, surgeon B was allowed to use a hand-held Doppler while surgeon C used an Acuson 128 (Acuson Corporation, Mountain View, California, USA) colour duplex scanner with a 7·5-MHz probe. Duplex assessment was performed with the patients upright and venous reflux was induced by relaxation following passive calf compression.

The surgeons were required to identify the superficial venous system involved (long or short saphenous) and determine the presence of saphenofemoral and/or saphenopopliteal incompetence. They were asked to commit themselves to one of the following management protocols:

1. Saphenofemoral ligation with stripping and avulsions.
2. Saphenopopliteal ligation and avulsions
3. Saphenofemoral ligation, stripping, saphenopopliteal ligation and avulsions.
4. Avulsions or sclerotherapy (if no evidence of saphenofemoral or saphenopopliteal incompetence)

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Results

Duplex assessment revealed saphenofemoral incompetence only in 48 limbs (68 per cent), saphenopopliteal incompetence only in nine limbs (13 per cent) whilst in six limbs (8 per cent) there was co-existing saphenofemoral incompetence and saphenopopliteal incompetence (*Table 1*). Although the varicose veins appeared to involve the long saphenous system in the remaining eight limbs (11 per cent), duplex assessment did not demonstrate saphenofemoral incompetence.

The biggest discrepancy between findings at traditional clinical examination with, or without Doppler ultrasonography, compared with those of duplex, occurred in limbs with saphenofemoral incompetence as well as saphenopopliteal incompetence. Based on the preoperative assessments, inappropriate surgery (as shown in *Table 1*) would have been performed in 14 limbs (20 per cent) and nine limbs (13 per cent) using clinical examination with a tourniquet and clinical examination plus Doppler ultrasonography respectively.

Discussion

The assessment and surgical management of varicose veins continues to be refined to improve the results of treatment. The need for meticulous technique performed by experienced surgeons has been stressed[2]. This study highlights the inaccuracies of traditional clinical examination techniques. Although accuracy is improved by the use of Doppler ultrasonography, the technique still fails in approximately one in every ten limbs (particularly when there is saphenofemoral incompetence as well as saphenopopliteal incompetence). Based on the findings of this study, cogent arguments can be made for the routine use of colour duplex scanning in the preoperative

Table 1 Results of preoperative assessments

Diagnosis	Proposed operation	No of limbs Duplex	Tourniquet +Doppler*	Tourniquet
Saphenofemoral incompetence only	SFL+S+A	48	49	46
Saphenopopliteal incompetence only	SPL+A	9	7	12
Saphenofemoral incompetence + saphenopopliteal incompetence	SFL+S+SPL+A	6	3	1
Long saphenous incompetence (no saphenofemoral incompetence)	A only	8	11	12

*One patient was not assessed by clinical examination with a tourniquet and Doppler ultrasonography. SFL, saphenofemoral ligation; SPL, saphenopopliteal ligation; S, stripping of long saphenous vein above knee; A, stab avulsions assessment of varicose veins in order to reduce the possibility of recurrence. However, the resources required to implement this are not insignificant and would only be made available if colour duplex assessment can be shown to reduce recurrence in a randomized trial.

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Flow cytometric analysis of p53 oncoprotein expression in cutaneous melanoma

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Background Mutation of the *p53* tumour suppressor gene is thought to represent a significant step in the development of over half of all human cancers. Qualitative investigations of p53 protein in cutaneous melanoma suggest that overexpression is more common than in other tumours. This study analysed p53 protein expression using flow cytometry as a quantitative assay.

Methods Expression of p53 protein was assayed in ten benign melanocytic naevi (BMN) and 50 surgically excised ethanol-fixed melanomas. Nuclei were stained for the p53 protein with Pab1801 and analysed using flow cytometry. Protein expression was further correlated with clinicopathological parameters.

Results None of the BMN was immunopositive for p53. Forty-one of the 50 melanomas stained positively. The overall median positivity for p53 in primary melanoma was 12·8 per cent compared with 22·5 per cent in metastatic disease. No association was found between p53 expression and Breslow thickness or presence of nodal and skin metastases. Overexpression of p53 was associated with ulceration, mitotic figures and lymphocytic infiltration, and there was a striking increase of p53 expression with age. Expression of p53 was inversely correlated with disease-free interval.

Conclusion Although overexpression of p53 is common in melanoma, there was no association with major clinical parameters such as Breslow thickness and overall survival. The association found between p53 and other clinicopathological features suggests that the tumour suppressor gene does play a role in the evolution of melanoma.

The worldwide incidence of cutaneous melanoma continues to rise at an alarming rate, almost doubling each decade[1]. Furthermore, this rise has particularly affected Caucasians under 40 years of age[1]. Unfortunately this change has not been paralleled by advances in therapy, and surgical excision of thin primary melanomas still offers the only possibility of cure.

Further advances in the management of this disease are unlikely to be made without greater understanding of melanoma biology. Considerable interest centres on the role of the nuclear tumour suppressor gene *p53*[2]. Mutation of this gene is associated with a wide range of human cancers of differing tissue origin[3,4] and the frequency of these mutations suggests it plays a central role in tumour biology[5,6].

Wild-type (normal) *p53* displays several features of a recessively acting tumour suppressor gene and is induced in response to a number of DNA injuring agents including ultraviolet light[7] and radiation[8]. The transforming action of other oncogenes, such as *ras*, is prevented by *p53 in vitro*[9,10]. This gene is principally concerned with genomic conservation during cell division, mediated by regulation of cell-cycle check points, particularly G1[11]. Overwhelming DNA damage induces cells to undergo apoptosis (programmed cell death)[11,12].

The emergence of a coherent model to explain the role and mechanism of *p53* has also been accompanied by the increasing awareness that *p53* gene mutation and changes in oncoprotein expression may provide clues to the aetiology of various cancers and may also be of prognostic significance[5,13,14]. These changes may be manifested in the level of expression and immunodetection of the p53 protein. Inactivation of the p53 protein produces a stable conformation with an increased half-life[15] that is detectable with appropriate monoclonal antibodies[16].

A limited number of immunohistochemical studies have investigated p53 overexpression in malignant melanoma, and have suggested that p53 oncoprotein is overexpressed to a greater extent in melanoma than in other tumour types[17]. Furthermore, the level of expression correlates with formation of the metastatic phenotype and prognosis[18–20]. Immunohistochemistry provides qualitative information on the architectural distribution of the p53 protein but provides little quantitative data. To obtain such data the present study used flow cytometry to clarify further the relationship between p53 oncoprotein expression in melanoma and its associated clinicopathological parameters.

Materials and methods

Specimens

Two types of melanotic specimens were studied, ten common acquired benign naevi and 50 melanomas from 50 patients undergoing excision of either primary lesions or locoregional metastases. Tumour specimens comprised 14 primary melanomas and 36 locoregional metastases. A portion of the fresh, dry sample was assigned to histological analysis and the remainder placed in 70 per cent ethanol and stored at 4°C until processed. Disease stage, tumour site, thickness of the primary melanoma and the presence of associated histological features such as ulceration, mitotic figures and lymphocytic infiltrate were all recorded.

Preparation and staining of nuclei

A 3-mm^3 sample of each specimen was minced and enzymatically enucleated in 10 ml pepsin 0·4 mg/ml solution in hydrochloric

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acid 0·1 mol/l (Sigma Chemical Company, Poole, UK). The mixture was constantly agitated at 37°C for 50 min and filtered through a 35-micron nylon mesh in a Swinnex holder. Nuclear concentration was adjusted to less than 10^6 nuclei per mm^3 and aliquoted into two samples before being washed twice in phosphate-buffered saline (PBS), centrifuging at 2000 r.p.m. for 5 min between cycles. One sample was used to assay p53 whilst the second served as an isotypic control using an immunoglobulin (Ig) G$_1$ antibody at the same protein concentration. Oncoprotein p53 was identified using Pab1801 (Cambridge Research Biochemicals, Cambridge, UK), which recognizes both wild-type and mutant p53 oncoprotein; Pab1801 was added at a dilution of 1:25 in a 100-μl solution of PBS containing 0·5 per cent normal goat serum and 0·5 per cent Tween 20 (polyoxyethylenesorbitan monolaurate; Sigma Chemical Company, UK) for 1 h at room temperature. The suspension was then washed in PBS and reincubated with goat antimouse IgG fluorescein isothiocyanate (FITC) conjugate (Sigma Chemical Company) for 30 min at room temperature. The mixture was finally washed in PBS and resuspended in 1 ml PBS containing ribonuclease A 1 mg/ml (Sigma Chemical Company) and 20 μl propidium iodide (Sigma Chemical Company).

Flow cytometry

Prepared samples were analysed on a FACScan flow cytometer (FACScan, Becton Dickenson, San Jose, California, USA). Data were analysed on 10 000 events (nuclei) for each sample by measuring the number of positively labelled cells compared with the control; the level of background positivity was adjusted to 1 per cent or less. Analysis was performed for the total population and for each cell-cycle phase by using appropriate computer-generated windows on the DNA profile.

Statistical analysis

Unpaired populations showing a normal distribution were compared using Student's t test. Survival curves were produced using the method of Kaplan and Meier[21], with significance being determined using the log rank test[22]. Survival data were analysed using JMP (SAS Institute, Cary, North Carolina, USA). Multivariate analysis was performed using Cox's proportional hazards model[23].

Results

Clinical data and pathology

Tumour samples were obtained from 30 female and 20 male patients, with a median age of 54·4 (range 20–93) years and median follow-up of 39 months. Tissue diagnosis was confirmed on formalin-fixed, paraffin-embedded sections stained with haematoxylin and eosin. Fourteen primary melanomas were investigated in this study, consisting of nine superficial spreading malignant melanomas and five nodular lesions, ranging in thickness from 1·0 to 7·0 (mean(s.d.) 4·0(2·2)) mm. Thirty-six metastatic melanomas were analysed, comprising ten skin metastases and 26 nodal secondaries. In patients whose metastases were analysed, data on the primary tumour were available for all but two who presented with secondary disease from an unknown primary.

Expression of p53 oncoprotein

Expression of p53 was recorded as percentage positivity of immunostained nuclei. A typical example of the flow cytometric profile of an aneuploid tumour stained for p53, and its control, is shown in *Fig. 1*. The majority of the positivity for p53 is found within the aneuploid population and is expressed throughout the cell cycle. In this example the positivity based on the control profile was 60·6 per cent.

Expression of p53 oncoprotein was detected in 12 of 14 primary tumours studied and 29 of the 36 metastases, overall representing 41 (82 per cent) of 50 tumour specimens assayed. None of the ten benign specimens stained positively for p53 oncoprotein compared with their controls.

The proportion of p53-immunopositive nuclei showed considerable variation between tumours. Within the primary melanomas, a median positivity of 12·8 (range 0–83·6) per cent of nuclei was found. In *Table 1*, primary melanomas have been divided on the basis of their thickness into two groups: those less than and those greater than 3 mm thick. Only five melanomas fell into the first group, of which four were positive for p53. In this small subgroup, 6·3 (range 0·4–83·6) per cent of nuclei stained positively for p53. Of the thicker primaries, eight of nine tumours stained positively for p53, with 14·7 (range 5·7–86·0) per cent of nuclei proving immunopositive. No statistical difference was found in the level of p53 staining between these two groups of primary melanoma ($P = 0·68$).

In samples of metastatic melanoma, a median of 22·5 (range 0·1–95·3) per cent of nuclei were found to be

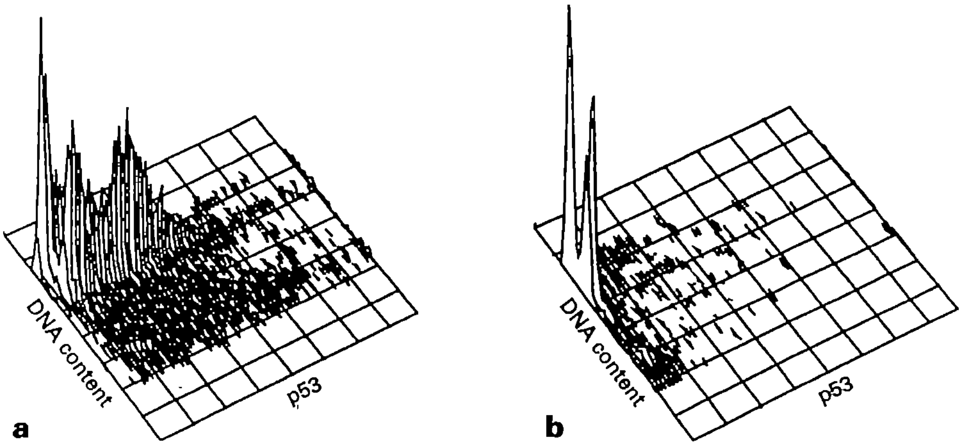

Fig. 1 Flow cytometric profiles of p53 expression obtained from an aneuploid malignant melanoma. a Specimen stained with Pab1801 and b isotypic control

Table 1 Expression of p53 oncoprotein in primary and metastatic melanoma measured by flow cytometry using Pab1801

Tumour type	No. of tumours	No. of p53-positive tumours	Median percentage of positive cells
Benign naevi	10	0 (0)	0
Primary melanoma			
<3·0 mm	5	4 (80)	6·3
>3·0 mm	9	8 (89)	14·7
Secondary melanoma			
Skin metastases	10	8 (80)	18·7
Nodal metastases	26	21 (81)	25·3

Values in parentheses are percentages

immunopositive. Metastases were subdivided into nodal ($n=26$) and skin ($n=10$) secondaries. Approximately 80 per cent of each type were positive for p53, with a median of 18·7 and 25·3 per cent of nuclei staining positively in skin and nodal metastases respectively ($P=0{\cdot}70$). Although there was an apparent difference in p53 level between primary and metastatic disease this was not statistically significant ($P=0{\cdot}41$).

Seven of 14 primary tumours and 17 of the 36 metastases were defined as aneuploid on the basis of their DNA profile. Expression of oncoprotein p53 did not vary with tumour ploidy. All benign lesions were diploid.

Histopathological parameters

In addition to tumour thickness, the association between p53 expression and certain histological parameters was examined (*Table 2*). Ulceration was present histologically in 14 of the primary melanomas. Expression of p53 oncoprotein was significantly higher in tumours derived from histologically ulcerated melanomas.

Mitotic figures (more than five per high-power field) were present in 25 of the melanomas analysed. Melanomas with mitotic figures had a higher median p53 positivity than those with no or few figures but this difference was not significant.

Lymphocytic infiltration of the primary or metastatic tumour was seen in 32 tumours and correlated with p53 level. Melanomas with histological evidence of infiltration or regression had a significantly higher p53 positivity than those without infiltration.

Clinicopathological parameters

The sex of the patient was not associated with p53 positivity. However, a striking relationship was found to exist, in this group of patients, between the age of the patient and p53 positivity of tumours. *Fig. 2* displays the incidence of p53-positive tumours against patient age; p53 positivity was uncommon in melanomas from patients under 60 years of age (*Table 2*). Within this group of patients ($n=26$) median p53 expression was 6·6 (range 0·1–91·9) per cent of nuclei per tumour. However, in melanomas from patients over 60 years of age ($n=24$) a median 57·0 (range 0·4–95·3) per cent of nuclei were immunopositive for p53. This difference was highly significant ($P=0{\cdot}0001$).

p53 positivity varied with primary tumour site, the highest levels being observed in head and neck lesions (61·9 per cent) followed by torso (25·3 per cent) and limb (18·7 per cent). These differences failed to reach statistical significance.

Table 2 Clinicopathological parameters and p53 positivity

Parameter	p53 positivity (%)	P^*
Tumour ulceration		
No	12·5	0·0001
Yes	64·1	
Mitotic figures		
<5 per h.p.f.	16·1	0·33
>5 per h.p.f.	32·9	
Lymphocytic infiltration		
No	12·5	0·017
Yes	52·5	
Patient age		
<60 years	6·6	0·0001
>60 years	57·0	
Disease-free interval		
<14·7 months	57·0	0·04
>14·7 months	15·4	

h.p.f., High-power field. *Student's *t* test

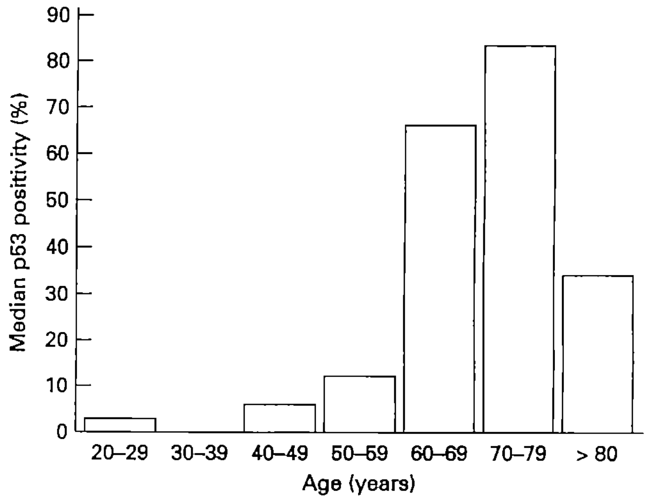

Fig. 2 Relationship between patient age and p53 positivity

The disease-free interval represents the period (in months) between diagnosis of the primary tumour and appearance of the first recurrence at any site. The median disease-free interval in this series was 14·3 (range 0–150) months. By univariate analysis the disease-free interval was found to act as a prognostic indicator ($P=0{\cdot}002$) but this was not significant on multivariate analysis. A statistically significant inverse relationship was found between p53 expression and disease-free interval (*Table 2*). In aggressive melanomas with a disease-free interval below median, p53 positivity was 57·0 per cent with a median value of 15·4 per cent in melanomas with a longer time to recurrence.

Patient survival

As expected multivariate analysis of survival data confirmed primary tumour thickness to be the major independent prognostic determinant. At a median follow-up of 39 months, no survival difference was found in this small group of patients between primary melanomas on

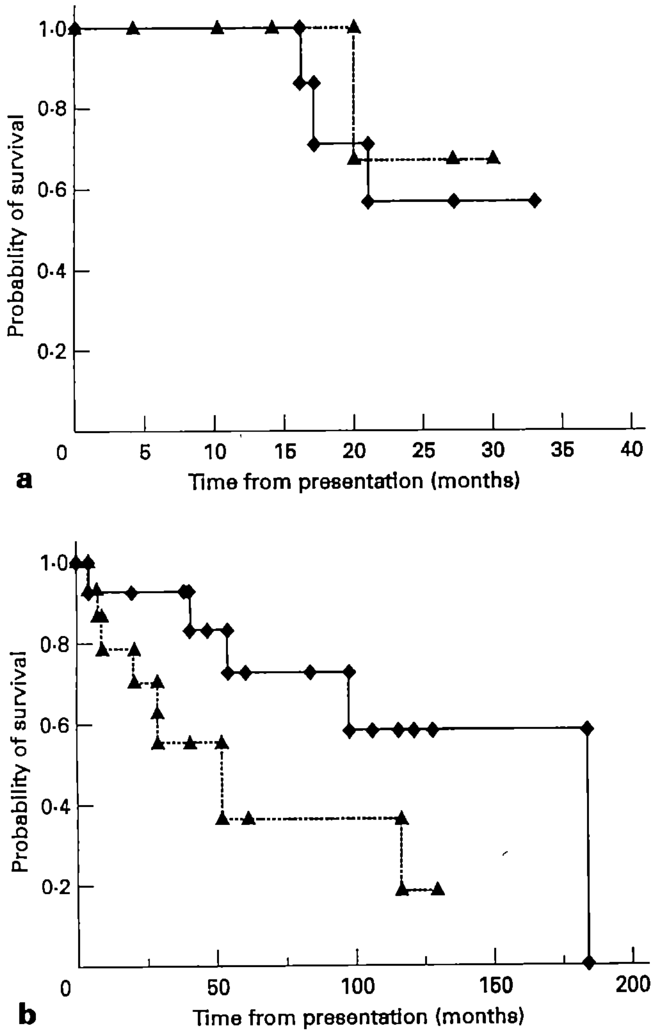

Fig. 3 a Expression of p53 and survival in patients who have primary melanoma with p53 protein positivity above median (——) or below median (——), $P = 0·95$. b Expression of p53 and survival in patients who have metastatic melanoma with p53 protein positivity above median (——) or below median (——), $P = 0·07$. Significance assessed using Kaplan-Meier analysis

the basis of p53 expression ($P = 0·95$) (*Fig. 3a*), although, in patients with locoregional disease, a trend was evident to suggest that patients with tumours of low p53 oncoprotein content showed improved survival compared with those who had tumours with high p53 oncoprotein content positivity ($P = 0·07$) (*Fig. 3b*). Patients with raised p53 expression (above median) were observed to have a shorter survival period (median 52 months) than those with lower p53 expression (median survival 120 months).

Further analysis suggested that raised p53 level was associated with poor prognosis in patients with metastases who had primary melanomas of 3 mm or more in depth but this was not statistically significant ($P = 0·07$).

Discussion

This study has shown raised expression of p53 oncoprotein to be prevalent in both primary and metastatic melanomas, and at an incidence higher than that found in almost any other tumour type. The relatively high prevalence of p53-positive melanomas has also been noted in immunohistochemical studies[17–19] in which an association between overexpression and poor prognosis has also been observed[18–20]. Lassam *et al.*[20] confirmed the observation of high oncoprotein levels in secondary lesions and, in particular, nodal metastases. However, only 5 per cent of primary melanomas were found to stain positively for p53 and all staining was intranuclear. It was concluded that p53 overexpression may be a late event in the progression of melanoma and of prognostic relevance, but is unlikely to act as a preneoplastic marker.

Whilst the number of tumours expressing p53 was high, the percentage of immunopositive cells in each melanoma was low. A similar low percentage positivity of p53-stained nuclei in melanoma was also observed by Cristolfolini *et al.*[24]. These findings suggest that detection of p53 protein is unlikely to follow clonal mutation in the *p53* gene. In early-stage melanoma development and radial growth-phase primary tumours, *p53*-mutation may be a focal event, whereas mutation of the gene itself may represent a late event in the development of the phenotype. The clinical correlates of this change require further study. The diversity of findings between this and other studies reflects the variation in samples, methods of preservation and analysis used in each. For definitive conclusions to be drawn the variables need to be standardized in a larger study. These findings suggest, first, that p53 oncoprotein expression is more prevalent in melanoma than in other cancers assessed with similar methods and, second, that overexpression may have a role in the development of the metastatic phenotype.

To date only one study has been published on the use of flow cytometric analysis of p53 oncoprotein in paraffin-embedded melanomas and this was confined to measurements in nodular melanomas. Akslen and Mørkve[25] found 29 of 30 tumours to be immunopositive for p53 using Pab1801, no association being found between the level of nuclear positivity and outcome. However, they observed significantly lower p53 protein levels in metastatic melanomas compared with primary tumours and speculated that this may be due to loss of the normal *p53* allele in progressing from primary to metastatic disease.

The significant association between raised p53 oncoprotein level and ulceration found in the present investigation suggests that growth deregulation involving loss of p53 function may allow more rapid tumour cell proliferation and ulceration as a secondary consequence. It is noteworthy that the groups of melanomas compared showed no statistical difference in thickness.

This study failed to identify any difference in p53 protein expression between primary and metastatic melanomas. However, a trend was observed between p53 expression and survival in patients presenting with thick tumours (more than 3·0 mm) and metastatic disease. This may imply that p53 overexpression is of prognostic importance in certain subgroups of melanomas which remain clinically and biologically distinct. Similarly, stabilization of the p53 protein may be important in developing the metastatic phenotype in these tumours and concurs with the immunohistochemical studies noted above, although a larger mutational analysis is required to assess and distinguish the relevance of genetic and oncoprotein activity to clinicopathological behaviour.

The significant association between oncoprotein expression and disease-free interval suggests that p53 deregulation may influence formation of metastases, although for the majority of tumours it may not affect their subsequent behaviour. In one other immunohistochemical study, p53 positivity in superficial spreading melanomas alone was associated with a prolonged disease-free interval[26]. In such thin tumours, this association may imply a protective role for p53, although the study did not distinguish whether the protein detected was wild type or stabilized.

The relatively high p53 positivity of head and neck melanomas compared with those situated elsewhere on the body may be due to increased sun exposure at this site, and the result of actinic damage. The rise in incidence of p53 overexpression that accompanied age in this group of patients is consistent with the concept that cancer is a multistep disorder in which the risk of achieving a critical, transforming gene mass increases with age. However, this association suggests that melanoma may arise in younger patients via mechanisms independent of p53 stabilization, i.e. deletion or mutation of other oncogenes[27], or inactivation of potential melanoma suppressor genes, i.e. 9p21[28,29].

Flow cytometry provides rapid, quantitative measurements of p53 oncoprotein level in ethanol-fixed melanomas, allowing assessment of distribution in relation to the cell cycle. Immunohistochemistry has the advantage of allowing study of the anatomical distribution of a protein, but is not quantitative or rapid. Flow cytometry overcomes these limitations and ideally both modalities should be used to assess protein localization and quantification.

The list of functions attributed to *p53* and the proteins that influence it is growing rapidly[30]. Elucidating the relevance of these factors with respect to clinical parameters may provide greater insight into cancer development in general and indicate new therapeutic possibilities.

Acknowledgements

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Totally stapled restorative proctocolectomy

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Background Totally stapled restorative proctocolectomy (TSRP) has simplified ileoanal pouch surgery but few reports exist concerning experience with the technique. A retrospective study of operative and functional data in a consecutive series of patients undergoing TSRP was undertaken.

Methods TSRP with J pouch formation was attempted in 103 patients between 1988 and 1995 (for ulcerative colitis (87 patients), familial adenomatous polyposis coli (nine), slow transit constipation (six) and hereditary non-polyposis colorectal cancer (one)). Three technical failures resulted in 100 patients available for assessment. Case notes were reviewed together with functional assessment by clinical interview and/or postal questionnaire.

Results Median operating time was 200 min, intraoperative blood loss 360 ml and hospital stay 12 days. There were no operative deaths. All but five patients (95 per cent) had loop ileostomy formation with subsequent reversal. There were 29 complications, six of which required further surgical intervention. Six pouches were excised and two patients had a temporary defunctioning ileostomy. Five patients were rediagnosed as having Crohn's disease, of whom four underwent subsequent pouch excision. Pouchitis (in the absence of Crohn's disease) occurred in eight patients (8 per cent). In 60 patients with at least 12 months of established function, median day and night stool frequencies were 5 and 1 respectively. Functional evaluation in 49 patients (82 per cent) revealed regular use of antidiarrhoeal medication in 21, urgency in 17, and total continence by day and night in 37 and 35 respectively. Fifty-three patients (88 per cent) were satisfied with the overall long-term outcome.

Conclusion TSRP is safe, has simplified a technically difficult operation and gives good long-term functional results.

Restorative proctocolectomy is now the treatment of choice for patients with ulcerative colitis requiring elective surgery[1] and is being used increasingly as a surgical option for the management of familial adenomatous polyposis coli (FAP)[2].

The initial descriptions of the operation which were complicated and technically demanding[3,4], involved retention of a long rectal stump with mucosectomy and a handsewn pouch–anal anastomosis. Although the early procedures suffered from high complication rates[3–5], progressive simplification of operative technique[6–14] has reduced the morbidity associated with restorative proctocolectomy. Arguably the simplest form of restorative proctocolectomy uses stapling instruments to fashion the pouch and pouch–anal anastomosis without performing an endoanal mucosectomy. While totally stapled restorative proctocolectomy (TSRP) is technically easier to perform than earlier restorative proctocolectomy procedures, there are few reports of its use and little is known about long-term function. The authors' operative experience with TSRP is described and the long-term functional outcome reported.

Patients and methods

Consecutive patients who underwent TSRP with formation of a pelvic ileal J reservoir between 1988 and 1995 were studied Preoperative diagnosis in these 103 patients was ulcerative colitis in 87, FAP in nine, idiopathic slow transit constipation in six and one case of hereditary non-polyposis colorectal cancer. Eighteen (21 per cent) of the 87 patients with ulcerative colitis underwent semiurgent surgery to treat fulminant disease. Twenty-seven patients (26 per cent) had previously undergone total colectomy with rectal stump preservation (21 with ulcerative colitis, two with FAP and four with slow transit constipation)

The operative technique involved diathermy dissection of the rectum, including the mesorectum, to the level of the upper anal canal with division approximately 1 cm above the dentate line using a stapling instrument (RL 30, Ethicon, Edinburgh, UK) Care was taken to identify and preserve the presacral nerves An ileal pouch was fashioned in the J configuration using two to three firings of a linear stapling device (PLC 75; Ethicon) ensuring that the apex of the J reached the upper anal canal without tension Anastomosis of the ileal pouch to the anal canal was then performed by the double-staple technique, using a detached head stapling instrument (CDH 29; Ethicon). Operative manoeuvres such as mucosal proctectomy, endoanal retraction and anal eversion were avoided. In all but five cases a temporary loop ileostomy was fashioned, ileostomy was avoided when technical difficulties prevented formation of a tension-free stoma. Patients received intraoperative subcutaneous heparin 5000 units and intravenous antibiotics (cefotaxime 1 g, metronidazole 500 mg) for 5 days after operation.

All patients were followed at a designated clinic at 3-month intervals in the first year and 6 monthly thereafter. Patients with functioning pouches for more than 12 months after closure of the ileostomy underwent detailed functional assessment, similar to that used by Weinryb and colleagues[15], by interview at an outpatient clinic and/or by postal questionnaire.

Operative mortality was defined as death within 30 days of surgery. Anastomotic leakage was defined clinically with features of pyrexia, lower abdominal pain and purulent discharge from the anus. Contrast studies were performed only when indicated clinically. The degree of continence was graded as normal, minor incontinence or major incontinence using standard clinical criteria[16] Urgency of stool was defined as the inability to defer defaecation for a minimum of 30 min[17]. Patients were considered to have pouchitis on the basis of diarrhoea with or without bleeding, the sigmoidoscopic appearance of pouch inflammation and the absence of specific pathogenic organisms in the pouch effluent Confirmation of the diagnosis was made by histological analysis of pouch mucosal biopsies[18]

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Results

TSRP was attempted in 103 cases but in three patients double stapling of the reservoir to the anal canal failed necessitating conversion to a handsewn pouch–anal anastomosis. The technical reasons for these conversions are summarized in *Table 1*.

There were no operative deaths. One patient committed suicide 4 months after surgery. The remaining 99 patients (53 male), median age 31 (range 9–59) years were available for assessment (*Fig. 1*).

The median follow-up was 31 (range 12–77) months. The median duration of surgery for TSRP in the 100 patients was 200 (range 70–285) min, median operative blood loss was 360 (range 50–2000) ml and the median duration of hospital stay was 12 (range 7–74) days. Elective closure of the loop ileostomy was performed at a median of 85 (range 9–660) days after TSRP.

Table 1 Details of patients who underwent attempted totally stapled restorative proctocolectomy with conversion to handsewn pouch–anal anastomosis at operation

Sex	Age (years)	Diagnosis	Technical reason
M	34	Ulcerative colitis	Inadvertent omission to fire gun after bowel division
F	25	Ulcerative colitis	Staple line opened during endoanal insertion of CDH stapling instrument
M	45	Ulcerative colitis	Rectal thickening precluded satisfactory cross-stapling

CDH, curved detached head

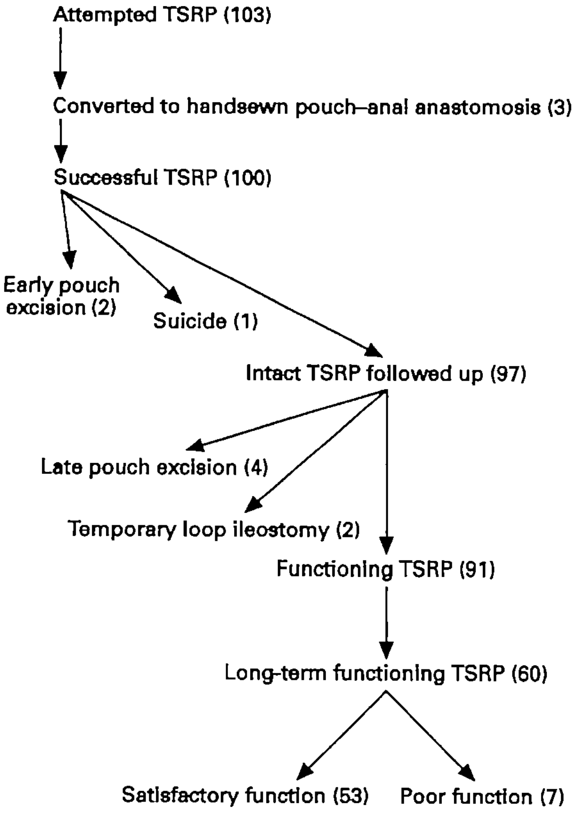
Attempted TSRP (103)
Converted to handsewn pouch–anal anastomosis (3)
Successful TSRP (100)
Early pouch excision (2)
Suicide (1)
Intact TSRP followed up (97)
Late pouch excision (4)
Temporary loop ileostomy (2)
Functioning TSRP (91)
Long-term functioning TSRP (60)
Satisfactory function (53)
Poor function (7)

Fig. 1 Outcome of 103 patients undergoing totally stapled restorative proctocolectomy (TSRP)

Early complications

Two pouches were excised during the early postoperative period, one because of ischaemia and the other because of haemorrhage.

Six patients developed clinical evidence of pouch/anastomotic leakage and/or pelvic abscess formation. In four of the six there was no covering ileostomy. Two of these four patients required formation of a loop ileostomy; the remaining four healed with antibiotic treatment and nutritional support.

Pulmonary thromboembolism occurred despite prophylaxis in two patients; both recovered fully.

Late complications

Complications associated with formation of a loop ileostomy are given in *Table 2*. Although 29 complication episodes occurred only six patients required further surgery.

Pouch–anal stenosis occurred in five patients (three female) and was treated by dilatation under day-case general anaesthetic. One patient developed a rare complication of complete pouch prolapse at the anus which was corrected by abdominal 'pouchopexy'.

Crohn's disease and pouchitis

Five patients (one male) considered initially to have ulcerative colitis have been shown subsequently to have Crohn's disease in the ileal pouch. Retrospective detailed review of the original colectomy specimen showed ulcerative colitis in four and indeterminate colitis in one, whilst the anastomotic 'doughnuts' showed no evidence of Crohn's disease. In four of these patients pouch excision was performed subsequently because of poor function and/or pouchitis

Eight patients developed clinical and histological evidence of pouchitis in the absence of Crohn's disease. Three individuals had more than one episode. Treatment was medical in seven, while one patient required a temporary ileostomy.

Table 2 Complications associated with loop ileostomy

Complication	*n*
After pouch construction	
Intestinal obstruction (conservative treatment)	3
Ileostomy obstruction (laparotomy)	1
Ileostomy retraction	3
Parastomal abscess	1
Excoriation at stoma site	1
High-output ileostomy	7
Total	16
After reversal of loop ileostomy	
Anastomotic leak (conservative management)	2
Anastomotic leak (ileostomy revision)	2
Intestinal obstruction (conservative treatment)	7
Intestinal obstruction (laparotomy)	1
Incisional hernia	1
Total	13

Pouch function

A temporary ileostomy was created in one patient because of poor pouch function. Of the 60 patients who fulfilled the criteria for long-term pouch follow-up, 49 completed a detailed questionnaire to assess pouch function. The remaining 11 patients were assessed, in detail, during regular outpatient review.

The long-term functional outcome is shown in *Table 3*. Approximately two-thirds of patients with established pouch function were, by their own assessment, leading normal lives. In contrast three of the 49 patients assessed had a poor functional result and were unable to work.

Genitourinary function

Three men developed retrograde ejaculation and one patient had partial erectile failure after TSRP. One woman noticed reduced libido, and a further three experienced pouch leakage during intercourse.

Table 3 Long-term functional outcome in 49 patients who had totally stapled restorative proctocolectomy

	Daytime	Night
Median (range) stool frequency	5 (2–16)	1 (0–4)
Continence*		
Total control	37	35
Minor incontinence	11	13
Major incontinence	1	1
Antidiarrhoeal medication*		
Never	22	
Occasional	6	
Regular ×1 medication	9	
Regular ×2 medications	10	
Regular ×3 medications	2	
Use of pads*		
Never	39	32
Sometimes	6	8
Frequently	3	3
Always	1	6
Urgency*		
None	32	
Urgency	17	
Fluid/flatus discrimination*		
Yes	37	
No	12	
Dietary adjustment*		
None	14	
Small changes	22	
Moderate changes	6	
Significant dietary restrictions	2	
Very substantial alteration	5	
Perianal irritation*		
Never	10	
1–2 episodes per week	22	
Every day	9	
Painful, cracked areas	3	
Open, raw bleeding areas	5	
Lifestyle disadvantages*		
None	18	
Undisturbed professional life, small changes to social life	15	
Undoubtedly affected professional and social life	9	
Definitely restricted professional and social life	4	
Unable to work, almost impossible to leave home	3	

*Values are numbers of patients

It was noted that 76 per cent of the women with established pouch function who had regular menstrual cycles detected a marked increase in pouch stool frequency just before and during menstruation.

Two patients had children following TSRP. Both were delivered by caesarian section.

Discussion

Restorative proctocolectomy has evolved since the first description of the procedure in adults in 1978[3]. Initially it was a time-consuming and technically difficult operation which involved performing a long mucosectomy with excision of the anal transitional zone. In addition the handsewn pouch–anal anastomosis required prolonged anal dilatation. The operation has since been progressively simplified with regard to pouch configuration and the avoidance of a long rectal stump. The relatively recent availability of stapling instruments has allowed the operation to be simplified further. Operative time has been reduced and prolonged anal canal dilatation avoided. TSRP might therefore be expected to yield improved functional results particularly with regard to continence and night leakage.

The results of the present study confirm that TSRP can be performed safely with short operative times, minimal blood loss and low morbidity. Further there is excellent long-term pouch function with a median stool frequency of 5 per day and 1 per night. This is in keeping with comparable series of totally stapled ileoanal pouches[19–22]. While one would not anticipate major differences in stool frequency between studies of handsewn and stapled pouches a difference in continence rates might be expected. In particular TSRP appears to avoid the troublesome complication of night leakage associated with the traditional operation. In the present series 76 per cent of patients were totally continent by day and only 26 per cent reported minor night leakage. In contrast, in a study of 389 patients who underwent handsewn pouch–anal anastomosis with mucosectomy, Pemberton and colleagues reported nocturnal soiling rates of 56 and 44 per cent in female and male patients respectively[23].

The leakage rates may be related to either the mucosectomy with excision of the anal transition zone or to prolonged anal dilatation. In a prospective pilot study comparing stapled and traditional techniques the Leeds group[7] found that 92 per cent of patients were completely continent after TSRP compared with only 58 per cent in the handsewn group. Moreover, whilst anal manometry showed normal anal canal pressures after TSRP, these were reduced in the handsewn group. Similar results have been reported in a retrospective comparative study from the Cleveland Clinic[24]. Others have suggested that TSRP is at least comparable to the handsewn operation[25,26] in terms of functional outcome. In an isolated but important prospective randomized trial of 32 patients from St Mark's Hospital, London[27], it was suggested that stapled pouches gave an inferior functional result to handsewn pouches. This study, however, did not comment on the important complication of night leakage which makes patients miserable by irritating the perianal skin. Those authors also had considerable experience and skill in the handsewn technique of pouch–anal anastomosis.

In the present series the clinical anastomotic leak rate was comparatively low at 5 per cent. This compares favourably with other series where the leakage rate ranges from 8 to 16 per cent[21,27,28] and may be attributed to the use of a defunctioning ileostomy in the majority of patients. Indeed, in the present series pelvic sepsis occurred predominantly in those patients who did not have a defunctioning ileostomy. The use of a diverting ileostomy does, however, have associated morbidity including dehydration, small bowel obstruction and risk of anastomotic leakage at closure. These complications have been reported by others[29-32] and also occurred in this series (*Table 2*). It is for this reason that the use of ileostomy has been abandoned or used only in selective cases by several groups[14,21,33-36]. While acknowledging these arguments the present authors continue to use routine loop ileostomy whenever technically possible, since pelvic sepsis is such a serious complication. Indeed, this experience with loop ileostomy for temporary faecal diversion after TSRP has, like others[37], been favourable with only 6 per cent of patients requiring surgery to correct ileostomy-related problems.

Other recognized technical complications of TSRP include the development of pouch–anal stenosis[19,27] and pouch–vaginal fistula[38,39]. In the present series the division of the upper anal canal was performed with a 30-mm diameter stapling instrument confirming full mobilization and resection of the rectum. If the 30-mm instrument cannot be easily accommodated this indicates inadequate dissection with residual rectum and necessitates further mobilization. In the present series there have been no pouch–vaginal fistulas.

The major late complication of restorative proctocolectomy is pouchitis which in the present series occurred in 13 per cent of patients, including five with Crohn's disease. This is comparable to other series[20,21,26,40,41] where the incidence varies from 12 to 30 per cent. Such variability may relate to differences in the definition of pouchitis. It has been suggested that pouchitis may be secondary to ischaemia[42] and since stapled pouch–anal anastomoses are under less tension than handsewn anastomoses this may explain the present relatively low figure for pouchitis. It was also found that pouchitis may indicate occult Crohn's disease[20]; 5 per cent of the patients in this series (five of 13 with pouchitis) had histologically confirmed Crohn's disease. Review of the original colectomy specimens, even with the benefit of hindsight showed ulcerative colitis in four and indeterminate colitis in the fifth. This suggests that even if a staged operation had been performed, Crohn's disease would not have been diagnosed. As such these data do not support the suggestion that patients should be treated by initial subtotal colectomy to avoid the risk of performing restorative proctocolectomy in the presence of occult Crohn's disease[20,43] However, a staged approach is used when the patient has other features suggestive, but not diagnostic, of Crohn's disease e.g. mouth ulcers or recurrent perianal sepsis. Given the inferior functional outcome after staged procedures[44] the use of on-table retrograde endoscopy of the small bowel may be a superior method of identifying occult Crohn's disease that is not recognized by standard preoperative investigations[45].

Arguably the greatest risk of TSRP is the retention of a short anal canal mucosal cuff with the risks of colitis, dysplasia and carcinoma In a study from the Cleveland Clinic, Florida[46] the incidence of inflammation and dysplasia in retained mucosa after TSRP for ulcerative colitis was assessed. In 35 per cent of patients the distal doughnut revealed ulcerative colitis at the time of pouch construction. At subsequent biopsy 43 per cent of these patients had persistent ulcerative colitis. No dysplasia was identified in any of these biopsies. Only one patient with evidence of ulcerative colitis on 'doughnut' and/or biopsy had symptoms attributable to active ulcerative colitis (2 per cent). In another series there were three reported cases of symptomatic colitis from the anal canal after TSRP[47] and this may prove to be the major long-term problem with the technique.

Leaving a short anal canal cuff in patients with FAP is perhaps more controversial. However, this appears to be an academic rather than practical argument since the risk of carcinoma in an easily surveyed 1 cm cuff will be small when compared with the benefits of superior functional outcome and the high risk of premature death in these patients from tumours at other sites. There have been no reports to date of carcinoma arising in the retained cuff of mucosa after TSRP.

Although this is not a randomized comparison of operative techniques the results of the present study confirm that TSRP has simplified a difficult operation and gives good long-term functional results, with particular regard to night leakage. Future careful follow-up is required, however, to ensure that there are no long-term complications associated with the short cuff of diseased mucosa which this technique leaves behind.

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Case report

Acute abdomen due to anthrax

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Intestinal anthrax is rare and rapidly fatal. To date, 11 sporadic cases have been reported[1]. Two patients survived but the other cases were fatal In addition, an epidemic including 18 cases of cutaneous anthrax and seven of intestinal anthrax was reported from India[2]. The present case is the first of intestinal anthrax where surgery was performed and the patient survived.

Case report

A 40-year-old woman from the southern part of Turkey developed chills and fever 3 days before admission. She admitted consumption of improperly cooked sausage several days before onset of the symptoms. On admission, she was restless, confused, dehydrated and afebrile. Her pulse rate was 136 per min, respiratory rate 28 per min and blood pressure 70/40 mmHg Her abdomen was distended and tense because of a massive amount of free fluid. She complained of constant generalized abdominal pain with rebound tenderness which was more severe in the right lower abdominal quadrant

Initial laboratory studies were: haemoglobin 21·3 g/dl; haematocrit 64 per cent; white blood cell count 11 200 per mm^3 (neutrophils 68 per cent, lymphocytes 23 per cent); serum sodium 125 mEq/l, serum potassium 3·7 mEq/l, serum chloride 84 mEq/l, urea 48 mg/dl; serum glutamic–oxaloacetic transaminase 36 units/l; serum glutamic–pyruvic transaminase 40 units/l. Serum amylase and lipase were within normal limits.

The aspirated ascitic fluid was semipurulent and turbid with a leucocyte count of 6000 per mm^3 (95 per cent neutrophils, 5 per cent lymphocytes), numerous erythrocytes and raised protein concentration. The fluid examined by Gram stain showed large, capsulated, Gram-positive non-sporulating bacilli in chains and pus cells. Large, grey, non-haemolytic colonies grew on blood agar. Cultures from this ascitic fluid yielded a pure growth of *Bacillus anthracis* The strain was identified on the basis of bacterial morphology, susceptibility to penicillin, carbohydrate fermentation, motility and Voges–Proskauer reaction. Identification was confirmed by animal (albino rat) inoculation test.

Oral intake of foods and fluids was stopped. The patient was given 1·5 litres plasma and 8 litres intravenous fluid in the first 24 h. Her blood pressure increased to 90/50 mmHg, but both the pulse (140 per min) and the respiratory (28 per min) rates remained unchanged. Some 16 h after admission, the preliminary diagnosis was obtained from Gram staining and the patient was treated with penicillin 4 million units every 4 h.

The next day the patient's bowel sounds disappeared and her abdomen became more distended and tender Rectal examination revealed a small amount of blood. At laparoscopy the peritoneal cavity was full of turbid fluid. Seven litres of ascitic fluid were removed by suction. The caecum and ascending colon were distended A confluent necrotic area was seen on the wall of the colon, but there was no perforation. The mesenteric lymph nodes were enlarged and petechiae were seen on the intestinal wall. All other viscera appeared normal. Laparoscopy was converted to open surgery and a right hemicolectomy with drainage was performed All layers of the right colon were very oedematous, the colonic wall was up to 4 cm thick. Vessels were maximally dilated with complete stasis and focal perivascular haemorrhage. Ulcers were seen in the mucosa of the colon.

Following the procedure the patient's condition improved. Blood pressure increased to 110/70 mmHg and pulse rate diminished to 112 per min. In the first 2 days, 1200 ml of ascitic fluid drained from the abdomen. On the eighth day, drainage stopped. No complications were seen after operation and the patient was discharged on the 15th day

Discussion

Intestinal anthrax is extremely rare, resulting from consumption of improperly cooked, infected meat. The diagnosis is very difficult and can be easily missed. Usually the stomach or right colon is involved[3]. Massive ascitic fluid has been seen in all reported cases of intestinal anthrax, possibly due to bacilli blocking perivascular lymphatics. Early diagnosis can be obtained from Gram stain of the ascitic fluid.

In one case of gastric anthrax, 5 litres of ascitic fluid were removed and temporary relief was experienced, but it was reported that ascites recurred rapidly and the patient died from hypovolaemic shock[4]. In the present experience, after the aspiration of ascitic fluid and removal of the involved viscus, the patient's condition improved rapidly. Recurrence of ascites was not very rapid, probably because the involved viscus had been removed.

Survival depends first and foremost upon the restoration of plasma proteins, fluid and electrolytes, and then maintenance of fluid and electrolyte balance. Previous authors[1,4] have reported that massive loss of fluid and electrolytes leads to renal failure which is the main cause of death in patients with intestinal anthrax treated with antibiotics.

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Outcome of 200 restorative proctocolectomy operations: the John Radcliffe Hospital experience

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Background Restorative proctocolectomy is now the operation of choice for the definitive management of ulcerative colitis and familial adenomatous polyposis (FAP).

Methods A total of 200 patients (117 male, 83 female) underwent restorative proctocolectomy over a 12-year period. Information in a dedicated prospective database was supplemented by chart review. Some 177 had ulcerative colitis, 13 had indeterminate colitis and seven had FAP. Pouch designs were two-loop J ($n = 142$), four-loop W ($n = 45$) and three-loop S ($n = 13$). The majority (73·5 per cent) had a stapled ileoanal anastomosis and 139 patients had a defunctioning ileostomy.

Results There were no deaths. Early morbidity (less than 30 days after operation) included 76 complications in 71 patients (35·5 per cent), of which 35 were related to the pouch itself. Long-term follow-up data were available for 196 patients at a median of 27 months. Sixteen pouches (8·0 per cent) have been excised. Mean daytime frequency was 4·5 (range 1–15). Of 175 patients with colitis, 42 (24·0 per cent) had one or more episodes of pouchitis.

Conclusion Continuous improvements in operative technique have simplified the procedure, and functional results, although variable, have generally been acceptable.

Restorative proctocolectomy was first described by Parks and Nicholls[1] in 1978 and has become the operation of choice for the definitive surgical management of ulcerative colitis and familial adenomatous polyposis (FAP). Continuous improvements in operative technique have simplified the procedure, and functional results, although variable, have generally been acceptable. The majority of patients are satisfied and living stoma-free lives.

The mortality rate approaches zero, but the incidence of complications remains high, the most common being pelvic sepsis, small bowel obstruction and pouchitis.

The aim of the present study was to evaluate the clinical and functional results of the first 200 consecutive patients with a pouch, operated on over a 12-year period at the John Radcliffe Hospital in Oxford.

Patients and methods

A total of 200 patients (117 male, 83 female) underwent restorative proctocolectomy between April 1983 and March 1995. Pouch operations were performed by three consultant surgeons (M G W.K., N.J.McC.M. and the late Emanoel Lee). Median age at the time of pouch surgery was 33 (range 6–67) years. A dedicated prospective database has been maintained of all patients undergoing restorative proctocolectomy which includes details of the patient's history, operation, postoperative morbidity, functional outcome and follow-up assessments. This paper reports a retrospective analysis of the information available in the database, supplemented where necessary by reference to the hospital notes.

Following pouch surgery patients were reviewed at 2–12 weeks, 3, 6 and 18 months, and annually thereafter. At each review, data concerning late morbidity and pouch function were obtained, and this included daytime and night-time frequency, presence or absence of incontinence, urgency and mode of pouch evacuation, use of antidiarrhoeal drugs and episodes of pouchitis. Sexual and urinary function were also assessed.

Incontinence was defined as major (gross leakage, wearing pads day and night) or minor (occasional faecal seepage, spotting of underclothes). Urgency was defined as an inability to defer defaecation for at least 30 min.

Pouchitis was defined as an increase in pouch evacuation frequency with endoscopic and histological evidence of acute inflammation.

Diagnosis and indication for surgery

The diagnoses are given in *Table 1*. Of seven patients with FAP, one had a preoperative diagnosis of severe dysplasia and one had an occult carcinoma. The main indication for operation in patients with ulcerative colitis was failed long-term medical treatment of the disease (50·3 per cent) and for indeterminate colitis an acute severe attack (nine of 13 patients) (*Table 2*).

All colonoscopic biopsy series or previous resection specimens were reviewed to minimize errors in histopathological diagnosis. Where there was continuing doubt over the possible diagnosis of Crohn's disease, a three-stage procedure was used in elective cases. Patients with active anal lesions such as perianal fissures or fistulas were excluded.

Operative technique and pouch design

The categories of pouch operations performed are shown in *Fig. 1*. In 123 patients (61·5 per cent) rectal dissection was performed in the mesorectal plane and in 77 (38·5 per cent) a close rectal dissection was performed. Three pouch designs were used during the series: the two-loop J pouch (142 patients (71·0 per cent)), the four-loop W pouch (45 (22·5 per cent)) and the three-loop S pouch (13 (6·5 per cent)).

The majority of patients, 147 (73·5 per cent), underwent a stapled pouch–anal anastomosis. Some 53 (26·5 per cent) had an endoanal handsewn anastomosis. In general, a stapled anastomosis was performed without mucosectomy. The extent of mucosectomy performed with a handsewn anastomosis reduced as the series matured. To date, the anal transition zone has been preserved in 165 patients (82·5 per cent) and removed in 35 (17·5 per cent).

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Some 139 patients had a defunctioning ileostomy fashioned at the time of pouch surgery, of which 129 had been closed at the time of analysis. The median time to closure of ileostomy after restorative proctocolectomy was 16 (range 4–103) weeks. Sixty-one patients underwent pouch surgery without an ileostomy.

The majority of patients (80·0 per cent) with ulcerative or indeterminate colitis were on steroid therapy at the time of surgery. All patients received prophylaxis for deep vein thrombosis (heparin 5000 units subcutaneously twice daily) and perioperative antibiotics (intravenous cephalosporin and metronidazole).

Results

Early morbidity after pouch surgery

There were no postoperative deaths in the series. Early morbidity (less than 30 days) included 76 complications in 71 patients (35·5 per cent). Of these, 35 (46 per cent) were related to the pouch procedure itself and the remaining 41 (54 per cent) were non-specific (*Table 3*).

Thirteen patients developed pelvic and intra-abdominal sepsis; six underwent further laparotomy to achieve adequate drainage, two were managed with computed tomography (CT)-guided drainage of the abscess and five were managed with antibiotic therapy alone. Pouch haemorrhage occurred in five patients: one pouch was excised for uncontrollable bleeding and refashioned; two were controlled by suturing or diathermy of the bleeding vessel; and two settled spontaneously. Three pouches were excised for ischaemia and these patients were left with a permanent ileostomy. Adhesive small bowel obstruction occurred in six patients, of whom five were on steroid therapy before operation and four required laparotomy.

Table 1 Preoperative diagnosis

Diagnosis	No. of patients	M:F
Ulcerative colitis	177	104:73
Indeterminate colitis	13	6:7
Familial adenomatous polyposis	7	5:2
Functional problems	2	1:1
Hirschsprung's disease	1	1:0

Table 2 Indications for restorative proctocolectomy

	Ulcerative colitis ($n = 177$)	Indeterminate colitis ($n = 13$)	FAP ($n = 7$)
Failed medical treatment	89 (50·3)	4	0
Acute severe attack	79 (44·6)	9	0
Severe dysplasia	6 (3·4)	0	1
Carcinoma	3 (1·7)	0	1

Values in parentheses are percentages. FAP, familial adenomatous polyposis

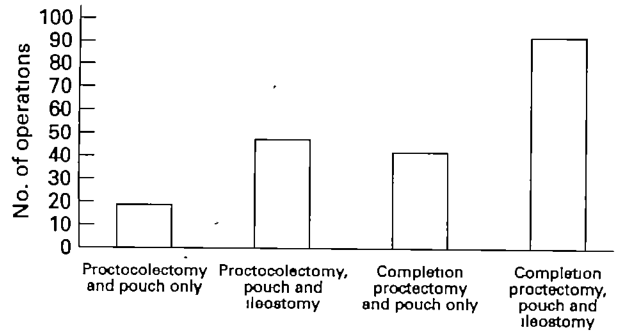

Fig. 1 Numbers of each type of restorative proctocolectomy operation performed

Long-term complications

Long-term follow-up data were available for 196 of the 200 patients at a median of 27 (range 0·5–139) months. Four patients are being followed elsewhere in the UK or overseas. During this period 65 complications were noted in 54 patients (27·6 per cent), as detailed in *Table 4*.

Anastomotic stenosis ($n = 17$), small bowel obstruction ($n = 16$), pelvic sepsis ($n = 7$) and pouch–vaginal fistula ($n = 6$) presented significant management problems.

Table 3 Early morbidity

Complication	No. of patients ($n = 71$)	Management: Surgery	Management: Conservative
Procedure specific			
Pouch haemorrhage	5	3	2
Pouch ischaemia	3	3	0
Intra-abdominal or pelvic sepsis	13	8	5
Small bowel obstruction	6	4	2
Small bowel perforation	1	1	0
Pouch–vaginal fistula	1	1	0
High ileostomy or pouch output	6	0	6
Non-procedure specific			
Paralytic ileus	3	0	3
Septicaemia	1	0	1
Wound sepsis	5	0	5
Wound dehiscence (superficial)	1	0	1
Bleeding from duodenal ulcer	1	1	0
Perforated duodenal ulcer	1	1	0
Other*	29	0	29

*Urinary tract infection, respiratory tract infection, psychiatric, etc.

Table 4 Long-term complications

Complication	No. of patients ($n = 54$)	Management: Surgery	Management: Conservative
Pouch–vaginal fistula	6	5	1
Pelvic sepsis	7	6	1
Pelvic collection of fluid	2	0	2
Small bowel obstruction	16	11	5
Incisional hernia	3	3	0
Enterocutaneous fistula	3	1	2
Anastomotic stenosis	17	17	0
High pouch output	1	0	1
Fistula *in ano*	4	1	3
Perianal abscess	2	2	0
Other*	4	0	4

*Depression, anal pain, addisonian crisis

Pouch excision

Sixteen (8·0 per cent) pouches have been excised. Four were excised within 30 days of surgery for haemorrhage ($n = 1$) or ischaemia ($n = 3$). The remainder were excised 5·5–71 (median 15) months after pouch surgery. The indications for excision are detailed in *Table 5*, the commonest cause being chronic pelvic sepsis. In three patients with indeterminate colitis a diagnosis of Crohn's disease was established at a later date.

Pouch function

Functional data were assessed for 183 patients with a functioning pouch. Seventeen patients were excluded: the four patients being followed elsewhere, three who had early pouch excision and ten awaiting ileostomy closure.

Median daytime stool frequency was 4·5 (range 1–15). Some 144 patients (78·7 per cent) reported passage of stool once or less at night. The distribution of stool frequency is detailed in *Table 6*.

Thirty-one patients presented with faecal incontinence (two major, 29 minor). Sixty-three patients (34·4 per cent) were clearly able to discriminate flatus from liquid or semisolid stools. The remainder enjoyed a varying degree of discrimination but only 20 patients (10·9 per cent) reported urgency. Fifty-two patients (28·4 per cent) continued to take antidiarrhoeal drugs. Functional outcome with regard to pouch design is shown in *Table 7*.

Table 5 Reason for pouch excision

	No. of patients
Haemorrhage	1
Ischaemia	3
Sepsis	4
Incontinence	2
Pouchitis	3
Crohn's disease	3

Table 6 Stool frequency in 183 patients

Frequency	Daytime*	Nocturnal†
0–1	2	144
>1–2	6	9
>2–3	33	10
>3–4	36	3
>4–5	43	2
>5–6	30	4
>6	33	1

*Median 4·5 (range 1–15); †median 0 (range 0–11)

Table 7 Pouch design and function in 183 patients

Type of pouch	Incontinence	Urgency	Spontaneous evacuation	Antidiarrhoeals
J ($n = 130$)	23	18	127	48
S ($n = 41$)	6	1	19	3
W ($n = 12$)	2	1	11	1

Bladder and sexual function

Some 178 (90·8 per cent) of 196 patients had normal bladder function. Five (4·3 per cent) of 115 men had sexual dysfunction: four complained of poor erections and one of retrograde ejaculation. Five (6 per cent) of 81 women complained of dyspareunia.

Pouchitis

Forty-two (24·0 per cent) of 175 patients with colitis and functioning pouches presented with pouchitis. Of these, 29 experienced one episode, six had two episodes, three had three episodes, three had four episodes and one experienced five episodes. The median duration of episodes of pouchitis was 21 (range 2–364) days. Standard treatment comprised a 2-week course of oral metronidazole and steroid enemas. Those who did not tolerate metronidazole were prescribed ciprofloxacin or ampicillin–clavulanic acid preparations. A few patients with chronic or recurrent pouchitis were treated with low-dose ciprofloxacin (250 mg daily) for 3 months. Three patients had the pouch excised for intolerable symptoms from resistant pouchitis.

Discussion

The principal advantage of restorative proctocolectomy over panproctocolectomy is avoidance of a permanent stoma. The procedure offers the opportunity to remove the diseased colon whilst preserving intestinal continuity, avoids long-term stoma-associated morbidity and, compared with ileorectal anastomosis, avoids the risk of carcinoma or recurrent proctitis in the retained rectum.

This series contained a higher proportion of patients with inflammatory bowel disease than many published series as there is a relatively small, local FAP practice. Patients undergoing urgent or emergency surgery for colitis usually undergo total abdominal colectomy as the first procedure, which allows for pathological confirmation of the diagnosis in the resected colon, provides time to return the patient to optimal nutritional and medical status, and permits the patient to experience and manage a stoma. Patients undergoing primary elective or secondary pouch procedures are offered preoperative counselling by a stoma therapist and have the opportunity to meet other patients with a pouch (Kangaroo Club members in an Oxfordshire patient support group). In addition, anorectal physiology studies and, more recently, anal ultrasonography are performed to ensure that the anal sphincter is intact and functioning normally. Age is not a factor in deciding to create a pouch.

The majority of patients in this series had a J pouch fashioned. It is the authors' belief that this design is technically the most straightforward and, to date, there has been no convincing published evidence of significant benefit from more complex constructions. The double-stapled technique now employed during pouch–anal anastomosis has largely eliminated the need for endoanal dissection and preserves the anal transition zone.

Despite luminal inspection of the pouch before leaving the theatre, five patients experienced significant early postoperative haemorrhage. It is the authors' policy routinely to decompress the pouch with a rectal catheter; this has the added advantage of providing early warning of any haemorrhage.

Pelvic sepsis appears to be the commonest early postoperative complication (range 0–25 per cent) in reported series[2–7] and the present experience (6·5 per cent) is consistent with these reports. Adequate drainage of sepsis is essential and may require formal laparotomy (six of 13 patients with early sepsis and two of seven with sepsis presenting after 30 days) or CT-guided drainage (two of 13 and four of seven patients respectively). Sepsis became the commonest reason for long-term pouch excision in the study. Excision of the pouch may be required to remove the source of sepsis in patients who have not responded to drainage and antibiotic therapy, or may be requested for poor function. Tissues involved by chronic sepsis heal by fibrosis, and pouch dysfunction presumably arises from loss of compliance of the reservoir.

Anastomotic stenosis (8·5 per cent) was the commonest long-term complication in the present series, in keeping with the reported incidence (5–18 per cent) in other series[2,5]. Most of these stenoses were diagnosed by examination before closure of the defunctioning ileostomy, and dilatation was performed at the time of closure. No patient needed revision of the anastomosis but several required repeated dilatation. Overall, 32 dilatations were carried out in 17 patients. There was no significant difference in the incidence of anastomotic stenosis between stapled and handsewn anastomoses ($P = 0{\cdot}64$, χ^2 test).

In common with other series[6,8] nearly one in ten patients required admission for adhesive small bowel obstruction. A high proportion of these required operative intervention (11 of 16), including two patients who required small bowel resection and anastomosis.

Pouch–vaginal fistula is a difficult problem to manage. In this series, one fistula healed with antibiotic therapy alone but the other five patients underwent an initial defunctioning ileostomy followed by surgical closure. One fistula recurred after closure and the patient was later diagnosed as having Crohn's disease, which led to excision of the pouch. Fistulas can occur into the vagina in a female patient or present as a perianal fistula. If the perianal fistula is superficial, it can be treated by fistulotomy. However, if it involves the sphincter complex the use of a seton technique may be preferable. Pouch–vaginal fistulas can be repaired via a transvaginal or transperineal approach[9,10].

The functional results in the present series were acceptable, with a median daytime stool frequency of 4·5. The majority of patients had an undisturbed night or needed to pass stool once at night, an important result in terms of quality of life. Quality of bowel control is probably more important than simple frequency. Few patients had significant urgency following the construction of the pouch and many enjoyed good or excellent discrimination.

It is of note that in four of five men with sexual dysfunction pelvic dissection was performed in the mesorectal plane, which may carry a higher risk of damage to the pelvic nerves than perimuscular pelvic dissection[11]. Clearly meticulous technique is required to minimize pelvic nerve damage. The cause of dyspareunia following pouch surgery is less well defined but presumably relates to healing tissues in the pelvis and alteration in the support provided for the posterior wall of the vagina. Two patients in this series enjoyed normal pregnancies after restorative proctocolectomy and both babies were delivered by elective caesarean section. Caesarean section may be a sensible option for patients with a pouch as vaginal delivery may compromise sphincter function sufficiently to precipitate continence problems.

The reported incidence of pouchitis following restorative proctocolectomy varies between 7 and 45 per cent[12–14]. If strict clinical, endoscopic and histological criteria are applied, the true incidence appears to be 10–20 per cent[2,14,15]. All three criteria were taken into account in diagnosing pouchitis in two-thirds of the present patients. In one-third, the diagnosis was made on the clinical presentation and endoscopic appearance of the pouch mucosa, without histological confirmation, and this may explain why the incidence in this series exceeded 20 per cent

A critical review of the postoperative outcome after restorative proctocolectomy compared with that following construction of a Kock pouch or permanent ileostomy has shown only a marginal benefit for the pouch[2]. All patients contemplating pouch surgery should be realistically counselled about the potential morbidity and possibility of long-term pouch failure. One of the continuing difficulties with pouch surgery is the inability, despite careful investigation, confidently to predict outcome for an individual patient. Restorative proctocolectomy is not a return to normality, but in patients who are motivated to avoid a permanent stoma, who are otherwise fit and who have good sphincter function, it represents a significant surgical advance.

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Case report

Spontaneous resolution of histologically proven liver metastases from colorectal cancer

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Spontaneous regression of adult solid tumours is rare, being reported most commonly in patients with hypernephroma and melanoma. A case of regression of metastatic rectal cancer is described.

Case report

In January 1983 a 69-year-old man presented with a 6-week history of altered bowel habit and weight loss. Physical examination showed a 5-cm hard liver edge and sigmoidoscopy revealed a tumour at 15 cm. Anterior resection was performed for a large mobile tumour at the rectosigmoid junction. Large (diameter greater than 7 cm) metastases were present in both lobes of the liver and a Tru-cut (Travenol Laboratories, Thetford, UK) biopsy was taken from a left lobe metastasis.

Histopathological examination confirmed the tumour to be a moderately to poorly differentiated adenocarcinoma with scirrhous stroma, infiltrating through the bowel wall to the serosa. There was extensive spread in extramural veins, metastases in all the lymph nodes sampled and tumour at the lateral margins of excision. The liver biopsy contained fibrous tissue infiltrated with irregular clumps of neoplasm consistent with metastatic adenocarcinoma. The patient was given no additional therapy and remained well until July 1984 when he developed haematuria. Cystoscopy and biopsy revealed a moderately differentiated transitional cell carcinoma of the bladder, which was treated by endoscopic resection.

Follow-up ultrasonography of the liver in September 1989 showed no abnormality. In 1994, contrast-enhanced computed tomography showed two abnormalities in the right lobe of the liver less than 1 cm in diameter and consistent with simple hepatic cysts. The left lobe was normal. The patient remains symptom-free after 10 years of follow-up. Review of the original histology confirmed the findings for both primary and metastatic disease.

Discussion

Spontaneous regression of a number of different types of cancer has been reported[1], although in many cases this was either a partial or temporary phenomenon. Commonly cited tumours include renal cell carcinoma, melanoma, choriocarcinoma and the childhood tumours, retinoblastoma and neuroblastoma[2]. Spontaneous resolution of metastases is less commonly reported but pulmonary metastases from renal cell carcinoma are known to resolve occasionally following nephrectomy[3]. Complete resolution of histologically confirmed metastatic colorectal cancer has, to the authors' knowledge, not been reported previously. The reasons for such regression remain speculative[4]. Differentiation is recognized in childhood and germ-cell tumours, leaving a residual benign mass. For the remaining tumours, suggestions range from removal of a source of trophic agents to an immunological effect. It has not been possible to identify any factor that may have been involved in the regression in this case, other than removal of the primary tumour.

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Perianal sepsis in children

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Background Perianal sepsis is a relatively common surgical problem in children and yet the contribution of rare aetiological factors, the frequency of fistula formation complicating perianal abscess, the significance of bacteriological findings and the optimum treatment of fistula *in ano* are poorly understood.

Methods A consecutive series of 58 children (51 boys, seven girls) with a perianal abscess or fistula attending a tertiary referral centre over a 4-year period was reviewed.

Results Thirty-eight children (34 boys, four girls), ranging in age from 1 month to 12 years, presented with an abscess. After treatment, three developed a further abscess but only four developed a fistula. Fistula formation only occurred in those with enteric bacterial infection. Of 24 children with a perianal fistula five required further surgery for recurrence, four of whom were initially treated by fistulotomy. In most patients, the fistula was simple, low and direct, and treatment by fistulectomy resulted in significantly fewer recurrences. Apart from Crohn's disease, identifiable aetiological factors were rare.

Conclusion Perianal sepsis is most common in otherwise healthy boys under 2 years of age. Abscess is best treated by incision and drainage, and fistulectomy is successful for the small proportion who develop a fistula.

Perianal abscesses and fistulas in children are not rare but few studies have attempted to document their clinical features[1]. It is generally accepted that male infants are most commonly affected and fistulas tend to be simple, low and direct. However, the contribution of rare aetiologies, the frequency of fistula formation complicating perianal abscess, the significance of bacteriological findings and the optimum treatment of fistula *in ano* are poorly understood. The aim of this study was to review a single centre experience of paediatric perianal sepsis during the past 4 years in an attempt to address these issues.

Patients and methods

Patients under the age of 15 years with a perianal abscess or fistula were identified from operating theatre registers and personal records and the case notes and pathology reports were reviewed. During the last year of the study the data were collected prospectively. Statistical analysis was by χ^2 with Yates' correction for small samples.

Results

Between January 1992 and April 1996, a total of 59 patients were identified; the case notes and pathology reports of 58 were available for analysis. The results are summarized in *Fig 1*.

Perianal abscess

Thirty-eight children (34 boys, four girls), ranging in age from 1 month to 12 years, presented with an abscess. Two-thirds of patients were under 2 years of age (*Fig. 2*). Three of the boys were referred with a recurrent perianal abscess after previously unsuccessful surgery and in another boy the abscess extended into the ischiorectal fossa. Abscesses were treated by incision and drainage, usually with a deroofing incision; in one case a chronic superficial abscess cavity was excised and another infant boy was treated with antibiotics alone after spontaneous discharge of the abscess. No attempt was made to identify or treat a concurrent anal fistula. Except in the boy with an ischiorectal abscess, packing of the abscess cavity was rarely performed and wound healing was simply monitored by the paediatric outreach nursing team.

Bacteriology swab results were available in 34 of 38 patients (*Table 1*). During a mean follow-up of 23 months (range 2 months to 4 years), three patients developed a further abscess (at the same site), successfully treated by local drainage, and four boys developed a perianal fistula. *Staphylococcus aureus* was isolated in two of the three children who developed a recurrent abscess and a coliform in the other. Bacterial isolates in the four boys who developed a perianal fistula comprised coliforms in two and a group C *Streptococcus* sp. and mixed enteric flora in one each.

Perianal fistula

Twenty patients were referred with a perianal fistula, 14 of whom had been previously treated elsewhere for a perianal abscess. A further four patients with a fistula were derived from the perianal abscess study group. Consequently, a total of 24 patients (21 boys, three girls) with an age range of 2 months to 14 years were identified; two-thirds were aged less than 2 years (*Fig. 2*). Of the girls with a perianal fistula, one aged 9 years and another at 14 years had Crohn's disease and the third was an 8-year-old girl who had undergone anorectal myectomy for chronic constipation 2 months previously. Multiple fistulas were present in four patients: both girls with Crohn's disease, a 5-year-old boy with Crohn's disease and a male infant with bilateral simple low fistulas.

Fistulas were distributed evenly around the anal circumference. Of 28 fistulas in 24 patients, 13 had an anterior external opening, nine were posterior and six

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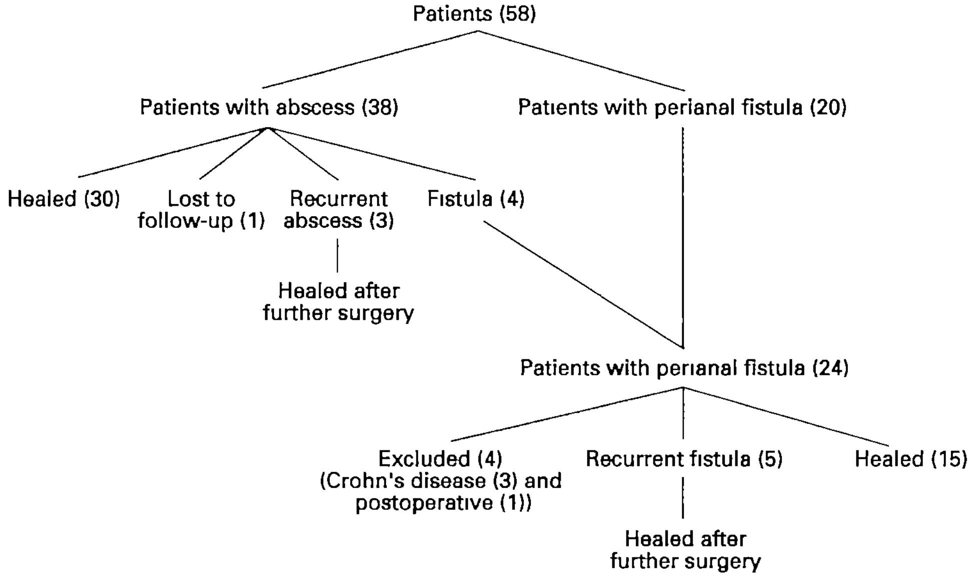
Patients (58)
Patients with abscess (38)
Patients with perianal fistula (20)
Healed (30)
Lost to follow-up (1)
Recurrent abscess (3)
Fistula (4)
Healed after further surgery
Patients with perianal fistula (24)
Excluded (4) (Crohn's disease (3) and postoperative (1))
Recurrent fistula (5)
Healed (15)
Healed after further surgery

Fig. 1 Outcome of 58 children presenting with perianal sepsis

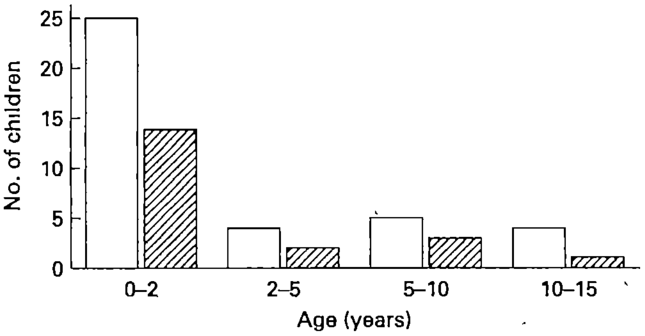

Fig. 2 Age distribution of 58 children with perianal sepsis. □, Patients with abscess; ▨, patients with perianal fistula

Table 1 Principal bacterial isolates from 34 children with perianal abscess

Bacteriology	No. of patients
Coliforms	15
Mixed enteric flora	7
Bacteroides fragilis	3
Group C *Streptococcus*	1
Staphylococcus aureus	7
No growth	1

were sited laterally at either 3 or 9 o'clock. All fistulas were simple, low and direct except for those in the three children with Crohn's disease (who also had fleshy skin tags and anal fissures) and the girl who had previously undergone myectomy. No additional aetiological factors were identified.

After excluding the four patients with more complex fistulas, nine children underwent excision of the fistula (ten tracts) and in 11 the fistula tract was laid open. There were five recurrent fistulas, four of which had initially been treated by fistulotomy. Fistulectomy was successful in all recurrences. In total, four of 11 tracts that were laid open recurred compared with one of 15 tracts that were excised ($\chi^2 = 5{\cdot}8$, 1 d.f., $P < 0{\cdot}02$).

Table 2 Rare aetiological factors in perianal sepsis in children

Crohn's disease
Anorectal surgery
Hindgut duplication
Neutropenia/chronic granulomatous disease
Immunodeficiency
Trauma (including sexual abuse)
Foreign body
Tuberculosis/actinomycosis
Munchausen by proxy
Anorectal malignancy
Diabetes mellitus

Discussion

Three important points emerge from this series. First, only four of the 38 patients with a perianal abscess went on to develop a chronic perianal fistula. Even if the child with a non-staphylococcal recurrent abscess is assumed to have had an underlying fistula the frequency of fistula formation after perianal abscess was only 13 per cent (five of 38 patients). This relatively low figure contrasts with rates of between 20 and 42 per cent in other paediatric series[2–7] but is comparable to values of between 4 and 31 per cent reported in adult patients[8]. Nevertheless, 18 of the 24 patients with chronic fistulas had a documented preceding perianal abscess. Many of these patients received antibiotic treatment before or after referral which might influence the natural history of fistula formation. Conservative treatment regimens which have included antibiotics have been associated with spontaneous fistula healing in some children[9]. As in adults, only those children with a perianal abscess due to infection by gut organisms developed a chronic fistula and not those infected by *Staphylococcus aureus*. The low incidence of subsequent fistula formation and the potential for harm should deter an attempt to identify and treat a concurrent fistula associated with a perianal abscess in a child.

Second, in contrast to some reports[3,5], specific aetiological factors appear to be uncommon in childhood perianal sepsis. Only four children had an identifiable cause for an abscess or fistula and three of these were older children with Crohn's disease. Perianal disease associated with paediatric Crohn's disease ranges in severity from anal fissure, skin tags, fistula and localized perianal abscess to extensive ischiorectal and pelvic suppuration[10]. Rare causes of perianal sepsis should be considered in children with recurrent or complex disease (*Table 2*)[3,5,11]. It is generally accepted that infection of a perianal gland is the cause of most perianal abscesses and fistulas in adults[12]. In children, perianal abscess and fistula have a striking male predominance and occur most frequently in infants under 2 years of age[2,5]. Fistula tracts are generally simple, low and direct, occurring around the whole circumference of the anus which supports the hypothesis of a predisposing congenital abnormality of the anal gland[12,13]. Fitzgerald *et al.*[14] suggested that an excess of androgen *in utero* causes the formation of abnormal anal glands which predispose to fistula formation. Pople and Ralphs[15] proposed that abnormally migrating cells from the urogenital sinus or the primitive hindgut might become trapped in the subcutaneous tissues of the perianal region during organogenesis leading to the formation of congenital sinuses close to perianal glands[15]. Others have argued for a developmental abnormality causing a focally irregular thick dentate line with deep crypts of Morgagni which retain bacteria and initiate cryptitis[16]. There is no compelling evidence to support any one of these hypotheses.

Third, this combined retrospective and prospective study suggests that the optimum treatment of fistula *in ano* in children is fistulectomy rather than fistulotomy. In adults, fistulotomy is the preferred option since wound healing is more rapid and there is less risk of sphincter disturbance whilst recurrence is rare[17]. Other paediatric series have identified recurrence rates of between 0 and 11 per cent after fistulotomy[6,9,14,16]. Fistulectomy may be advantageous because the wound is saucerized more effectively which discourages skin bridging, because the internal orifice of the fistula is more likely to be excised, or because no residual fistula tract remains. Postoperative anorectal function was not formally studied in these patients but none of the parents has reported disturbances of faecal control in the child at follow-up visits.

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Laparoscopic resection of the colon and rectum for cancer

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Background Laparoscopically-assisted resection for large bowel cancer is technically feasible. Sixty-six patients who had resection of the colon or rectum for cancer have been audited prospectively.

Methods Clinical and pathological data were collected prospectively as part of the ongoing Concord Hospital colorectal cancer project. Patients were followed up for a median of 29 months.

Results In 57 of 66 patients in whom laparoscopic resection was attempted the operation was completed laparoscopically. Three patients died from perioperative myocardial infarction. The median postoperative stay was 14 days. There was a high incidence of postoperative respiratory and cardiac complications. One patient developed a port-site metastasis.

Conclusion There was no obvious benefit from laparoscopically-assisted resection of large bowel cancer in these patients.

Since 1987 when Phillip Mouret described laparoscopic cholecystectomy[1], there have been numerous reports on the use of laparoscopic techniques for various abdominal operations including colorectal operations. Although the feasibility of many laparoscopic colorectal procedures has been established, there are serious concerns about the application of these techniques for patients with colorectal cancer[2–5]. Doubts have been raised regarding the adequacy of cancer clearance, the incidence of local recurrence and long-term survival. Furthermore, an increasing number of reports of port-site recurrence have added to these concerns[4,6,7].

Since 1991 66 laparoscopically-assisted colorectal procedures have been performed in this unit for cancer. The authors' experience with this group of patients is reported.

Materials and methods

Between October 1991 and September 1994 morbidity, mortality and pathology data on all patients undergoing laparoscopically-assisted resection for colorectal cancer were collected prospectively in a form suitable for computer storage and analysis as part of the ongoing Concord Hospital colorectal cancer project[8]. Follow-up was available on all patients to the end of September 1995. Patients received preoperative orthograde bowel preparation in addition to standard thromboembolic and antibiotic prophylaxis. The techniques for laparoscopically-assisted right and left hemicolectomy and abdominoperineal resection have been described in detail previously[9].

One pathologist (R.C.N.) who was unaware that the procedure had been performed laparoscopically examined and reported on all the specimens. The method of handling of pathology specimens has been described elsewhere[10]. The distance from the tumour to the proximal and distal margins of resection was measured in the fresh unfixed samples Tumours were staged using a clinicopathological (CP) staging system[8]. Morbidity and mortality data were reported on an intention-to-treat basis.

Operating theatre utilization time was defined as the time from entry into the anaesthetic room to the time the patient left the operating room. For purposes of hospital length of stay (measured as the number of postoperative days in hospital), patients were grouped into three principal groups: right colectomy (tumours from the caecum to the splenic flexure), left colectomy (tumours from the splenic flexure to distal rectum) and abdominoperineal resection (tumours considered unsuitable for a restorative resection).

Generalized anastomotic leakage was defined as that requiring laparotomy. A localized leak was a clinically and radiologically confined leak that either resolved spontaneously or was treated by conservative means.

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Results

Between October 1991 and September 1994, 66 patients had a laparoscopically-assisted resection for colorectal cancer at Concord Hospital. There were 38 men and 28 women with a mean age of 73·5 years. *Table 1* summarizes the procedures attempted in the 66 patients. In nine patients (14 per cent) the procedure was converted to an open operation. Conversion was required because of lack of progress after a trial dissection in two patients, and in one patient for each of the following reasons: port injury to caecum; dense intra-abdominal adhesions; tumour adherence to the abdominal wall; tumour invasion of the duodenum; hypercapnoea; inability to identify the ureter; and bleeding from the posterior aspect of the prostate.

The operating room utilization time and median length of hospital stay are detailed in *Table 2*.

Table 1 Laparoscopically-assisted operations for colorectal cancer

Operation	No. completed	No. converted
Right hemicolectomy	34	6
Transverse colectomy	1	0
Left hemicolectomy	3	0
Sigmoid colectomy	6	2
Anterior resection	2	0
Hartmann's operation	2	0
Abdominoperineal resection	8	1
Total colectomy and ileorectal anastomosis	1	0
Total	57	9

Table 2 Operating theatre time and length of stay by type of resection

Operation	Operating room utilization (h)	Length of stay (days)
Right colectomy ($n = 41$)	3·9 (3·3–6·7)	12·5 (8–50)
Left colectomy ($n = 15$)	4·4 (2·3–8·4)	16·0 (11–69)
Abdominoperineal resection ($n = 9$)	5·7 (3·4–7·3)	16·0 (10–78)

Values are median (range). One patient who had a total colectomy is excluded

Table 3 Postoperative complications following laparoscopic resection of colorectal cancer

Complication	n
Cardiac complication	12 (18)
Respiratory complication	9 (14)
Wound infection	8 (12)
Urinary tract infection	4 (6)
Renal impairment	4 (6)
Haemorrhage (requiring transfusion)	2 (3)
Small bowel obstruction	2 (3)
Pulmonary embolus	2 (3)
Septicaemia	1 (2)
Abdominal abscess	1 (2)
Anastomotic leakage (localized)	1 (2)
Prolonged perineal sinus (> 6 weeks)	1 (2)
Deep vein thrombosis	1 (2)

Values in parentheses are percentages

Three patients died after operation, all from myocardial infarction; two following right colectomy and one following left colectomy. The postoperative complications are listed in *Table 3*. The most common complications were cardiac and respiratory. Cardiac complications consisted of transient arrhythmias in eight patients, fatal perioperative myocardial infarction in three and cardiac failure in one. Nine patients developed postoperative respiratory complications. Four patients required antibiotics for chest infections, three patients with pulmonary atelectasis were treated by physiotherapy alone and two patients developed sputum retention of whom one required ventilation. Two patients, both of whom had a previous history of thromboembolic disease, sustained postoperative pulmonary emboli. One patient developed a localized anastomotic leak following sigmoid colectomy.

The pathological data are summarized in *Table 4*. Of the 66 colorectal cancers 13 were stage A, 26 stage B, 19 stage C and eight stage D owing to the presence of hepatic metastases (substage D_2). In no specimen was the surgical margin involved with tumour (substage D_1). In particular, the circumferential resection margin was clear of tumour in all 12 rectal cancer specimens.

Median follow-up was 29 months and all patients have been followed for a minimum of 12 months. As of the 30 September 1995, 43 patients are alive. Three have died from myocardial infarction within 30 days of operation, and a further five patients died from respiratory tract-related causes since discharge. Fifteen patients have died from colorectal cancer since leaving hospital. No patient has developed a local recurrence.

Table 4 Pathological data of operative specimens after laparoscopic resection of colorectal cancer

Operation	Right colectomy ($n = 41$)	Left colectomy ($n = 15$)	Abdomino-perineal resection ($n = 9$)
Size of primary lesion (cm)	4·5(2·2)	4·1(1·4)	3·6(1·0)
Proximal margin (cm)	9·9(6·1)	13·5(4·5)	24·3(6·9)
Distal margin (cm)	10·5(5·7)	13·5(4·5)	3·3(2·1)
Node harvest	17·6(10·0)	11·9(6·3)	10·0(5·2)

Values are mean(s.d.)

One patient developed a port-site recurrence, a 65-year-old man with a 4·5-cm tumour of the lower third of the rectum who had an abdominoperineal resection. The tumour was of average grade and was not perforated during surgery. It extended beyond the muscularis propria by direct spread and at one point was very close (0·46 mm) to the lateral line of resection. None of the 15 lymph nodes examined contained tumour. This was a CP stage B tumour. Twelve months after operation, the patient developed a 1-cm nodule in a right iliac fossa port site. Fine-needle biopsy confirmed adenocarcinoma. There was no evidence of recurrence elsewhere nor were metastases detected either on clinical examination or by abdominopelvic computed tomography. This was confirmed at laparotomy and a radical excision of the anterior abdominal wall was performed. Histological examination of the nodule confirmed a moderately well differentiated adenocarcinoma of colonic origin with extensive infiltration of the subcutis and skeletal muscle of the abdominal wall, extending to but not breaching the peritoneal surface. The patient remains well and tumour free 12 months following radical excision.

Discussion

Following the successful introduction of laparoscopic cholecystectomy, a number of reports of laparoscopic colorectal operations have appeared in the literature[11–14]. Many of these reports confirmed the feasibility of the use of laparoscopy to perform a bowel resection and predicted a significant advantage in terms of diminished postoperative pain, length of stay and a significant cost benefit[11,13,16,17]. In the context of the treatment of malignant disease, however, issues of cancer clearance, local recurrence and survival have emerged as principal concerns. Furthermore, there have been several reports of port-site recurrences[4,6,7] which have reinforced the concern about using laparoscopic techniques in patients with cancer.

This study reaffirms the technical feasibility of performing a laparoscopic resection in patients with colorectal cancer. There have been few operative complications, none of which have had serious sequelae. This underlines the importance of extensive training in a skills laboratory before embarking on a clinical programme and emphasizes that the principles of endosurgery should be no different to those of open surgery. The incidence of significant postoperative morbidity compares favourably with reports of the complications and deaths observed following open surgery for colorectal cancer in this institution[18]. Nevertheless, the results are clearly not superior to those obtained by open operation. Significant respiratory and cardiac complications occurred in 14 and 18 per cent of patients respectively.

This audit has highlighted some of the disadvantages of laparoscopic colonic resection. The median operating time in this series was long. Several authors have previously reported a significantly longer operating time for laparoscopic compared with open colorectal surgery[4,13,16]. Although this may be related to learning a new technique, it is likely that the operating time for laparoscopic surgery will remain significantly longer.

The median length of stay in this study was 14 days. Of note is that nearly a quarter of the patients in this series were 80 or more years of age, a group in whom early discharge could not reasonably be expected. There are several reports from North America suggesting that length of stay may be reduced using laparoscopic techniques[12,17,19]. Such reductions have not been achieved universally, with reports of no decrease or a non-significant reduction in other published studies[5,13].

Although the data presented here are uncontrolled, the authors have previously shown that the histopathological parameters in patients undergoing laparoscopically-assisted right hemicolectomy are not obviously different from those in patients having a traditional open procedure either in terms of margin of resection, lymphovascular clearance or CP stage[20]. Furthermore, it would seem that a radical cancer clearance operation need not be compromised by adopting laparoscopic techniques[12,21]. As lymph node harvest has not been validated as a marker of the adequacy of cancer clearance, only long-term outcome data will serve to answer this question.

Port-site recurrence is an intriguing complication which could potentially delay the development and application of laparoscopic surgery for patients with cancer. Wound recurrence following open surgery for colorectal cancer is a very rare complication[22] and its occurrence in patients who have a potentially curative resection cannot be dismissed lightly. Various hypotheses have been proposed to explain port-site metastases.

Skinner *et al.*[23] have demonstrated the viability of colorectal cancer cells obtained from luminal, mesorectal, serosal and post-dissection washes in colorectal cancer specimens. Leather and colleagues[24] detected free malignant cells in the peritoneal cavity of 15 of 35 patients undergoing open resection for colorectal cancer, and in 11 of these malignant cells were identified in washouts after resection. It is reasonable to suggest that such cells may be responsible for port-site metastasis.

Another possible explanation is that cancer cells gather on instrument tips during dissection and are deposited by them into port-sites[25]. Areas of tissue trauma are known to act as preferential sites for metastatic growth of cancer cells in animal models[26], possibly due to the release of macrophage growth factors. This may well explain why in the present patient with port-site metastasis, the recurrence was in the subcutis and muscle but did not involve the peritoneal surface. Another alternative explanation is that the pneumoperitoneum has an aerosol effect on cells in the abdomen, depositing them on to fresh wounds at port sites. Whatever factors are responsible for the development of port-site recurrence, this problem must be researched and understood if laparoscopic resection is to be applied as a viable alternative technique to open operation for patients with colorectal cancer.

In a previous study, the higher cost and increased utilization of operating room facilities associated with laparoscopic surgery for colorectal cancer was reported[27], and the authors remain unconvinced that the purported benefits of such operations have been realized. Furthermore, the spectre of the hitherto uncommon wound recurrence and the unknown long-term outcome of patients with colorectal cancer treated by laparoscopic resection suggests that considerably more research and development is needed before this technique can be applied universally to the surgical treatment of bowel cancer.

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p53 and K-*ras* status in duodenal adenomas in familial adenomatous polyposis

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Background The genetic alterations in patients with familial adenomatous polyposis (FAP) and duodenal adenomas are poorly characterized when compared with data relating to colorectal tumorigenesis in the same patients.

Methods Point mutation of the K-*ras* oncogene and point mutation and overexpression of the *TP53* tumour suppressor gene were investigated in 32 duodenal polyps (seven without mucosal pathology, 23 with mildly dysplastic adenomas and two with moderately dysplastic adenomas) from 21 patients with FAP.

Results K-*ras* mutation, *TP53* mutation or positive p53 staining were not found in duodenal polyps without histological abnormality. Of 25 duodenal adenomas, K-*ras* mutation was found in three (two mildly dysplastic, one moderately dysplastic), 20 showed positive p53 immunostaining, and mutation of the *TP53* gene was found in one moderately dysplastic adenoma. p53 protein overexpression in duodenal adenomas was significantly more frequent than mutation of either K-*ras* or *TP53* ($P < 0{\cdot}01$).

Conclusion p53 dysfunction is a hallmark of duodenal adenomas in patients with FAP. Overexpression may indicate DNA damage and thus an early step in tumorigenesis.

Patients with familial adenomatous polyposis (FAP) inevitably develop only a limited range of internal malignancies, particularly colorectal[1] and duodenal[2] cancer, despite the inherited genetic lesion being found in every somatic cell. Increased susceptibility to endogenous or exogenous carcinogens in the gastrointestinal tract might account for this observation. The high incidence of duodenal adenoma and cancer in these patients[2–4], coupled with evidence of their clustering around the ampulla of Vater[3], suggests the presence of a carcinogen in the bile of patients with FAP. A high level of DNA adduct formation in the FAP duodenum[5] and the carcinogenic effect of bile taken from patients with FAP on rat intestinal mucosa[6] support this supposition.

p53 plays a central role in the control of the cell cycle, DNA replication and the triggering of programmed cell death[7]. Nuclear accumulation of p53 after ultraviolet irradiation, γ irradiation or DNA-damaging agents suggests that p53 acts as a checkpoint to inhibit the replication of damaged DNA[8–10]. When the checkpoint fails, malignant change is more likely.

Elucidation of the genetic events in the duodenal adenomas found in most patients with FAP[3] provides an opportunity to investigate early genetic dysfunction including the initial responses to DNA damage, because duodenal adenomas are precancerous lesions[11]. p53 protein and *TP53* gene alterations as well as K-*ras* mutation were therefore investigated in duodenal adenomas from patients with FAP.

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Patients and methods

Materials

Endoscopic biopsies were taken from 32 polyps in 21 patients with FAP (14 men and seven women of mean age of 45 (range 26–68) years). Endoscopic findings were recorded using a video system following a protocol described elsewhere[3]. Three biopsies were taken from each polyp, two of which were snap-frozen in liquid nitrogen immediately for DNA work, while the third biopsy sample was fixed in 10 per cent formalin overnight for pathological and immunohistochemical study The polyps were classified according to previously described criteria[12].

*K-*ras *mutation analysis*

DNA was extracted with proteinase K and phenol–chloroform followed by ethanol precipitation[13].

The presence of K-*ras* point mutation was determined in the first two base pairs (bp) of codon 12 (CGT = Arg, GTT = Val, GAT = Asp, TGT = Cys) by the amplification refractory mutation system (ARMS; Cellmark Diagnostics, Abingdon, UK) using mismatch primers[14].

After the DNA was subjected to 35 cycles of polymerase chain reaction (PCR) (94°C, 60°C and 72°C for 2 min each) and amplified, PCR products were separated on an agarose gel. Samples containing K-*ras* mutant allele were detected by the presence of an additional band (158 bp for GGT and GAT mutations, or 191 bp for CGT and TGT) between two control PCR product bands (121 and 360 bp).

TP53 *analysis*

TP53 gene mutation was investigated in exons 5–8 using the technique of PCR-single-strand conformation polymorphism (PCR-SSCP)[15].

Briefly, 100 ng sample DNA was subjected to 35 cycles of PCR (95°C, 57°C, 72°C for 0·5, 2 and 1·5 min respectively) and amplified in 50 μl containing Tris–hydrochloric acid 10 mmol/l (pH 8·8), magnesium chloride 1·5 mmol/l, potassium chloride 75 mmol/l and 200 μmol/l deoxynucleotide triphosphates with 1 μmol/l of each primer and 1 unit of Taq polymerase After checking the PCR products on an agarose gel, a further 15 cycles of PCR were performed in the presence of [^{32}P]2′-deoxyadenosine 5′-triphosphate. Some 4 μl of the PCR product was diluted in 4 μl stop solution, denatured at 95°C for 3 min, placed on ice for 30 s and loaded on a 6 per cent polyacrylamide–bisacrylamide gel with 5 per cent glycerol for electrophoresis for 16 h at 12 W at room temperature.

p53 overexpression

Formalin-fixed paraffin-embedded sections were all processed in one batch for p53 immunohistochemistry by the standard method of streptavidin–biotin complex method with microwave antigen retrieval[16]. After endogenous peroxidase was inhibited in 0·5 per cent hydrogen peroxide in methanol, sections 4 μm in thickness were boiled in 0·01 mol/l citric acid (pH 6·0) in a microwave oven for 30 min. Sections were incubated with 10 per cent normal rabbit serum for 20 min before incubation with mouse monoclonal antibody DO7 (NCL-p53-DO7; Novocastra Laboratories, Newcastle, UK) for 45 min, followed by immunodetection with streptavidin–biotin[16].

A positive result was defined as diffuse brown nuclear staining involving more than 30 per cent of the epithelial cells without stromal staining[16]. The sections were assessed independently by three investigators. When the interpretation was agreed among investigators, the section was considered positive.

Results

Histopathology

Of the 32 polyps biopsied, 25 were adenomas (23 with mild dysplasia, two with moderate dysplasia) and seven showed no histological abnormality.

K-ras *point mutation*

Mutations were not found in K-*ras* codon 12 in the seven histologically normal polyps. Of 25 adenomas, three showed point mutations, two of which were mutated to Asp (GAT) (a mildly dysplastic tubular adenoma and a moderately dysplastic tubular adenoma) and one was to Cys (TGT) (a mildly dysplastic tubular adenoma) (*Fig. 1*).

TP53 *gene mutation in exons 5–8*

Of 25 adenomas, only one with moderate dysplasia harboured a *TP53* mutation, in exon 6 of *TP53* (*Fig. 2*) This adenoma showed positive p53 immunostaining; 96 per cent of adenomatous cells showed positive p53 staining, 48 per cent of which was strong and intense.

p53 overexpression. None of the histologically normal polyps showed positive p53 staining. Of 23 mildly dysplastic adenomas, 18 showed definitive positive staining by the authors' criteria (*Fig. 2*) (*Table 1*). All three adenomas with moderate dysplasia or a villous component (two moderately dysplastic adenomas and one tubulovillous adenoma) showed positive p53 immunoreactivity. One of two adenomas with moderate dysplasia showed intense positive staining and carried a *TP53* gene mutation (*Fig. 2*).

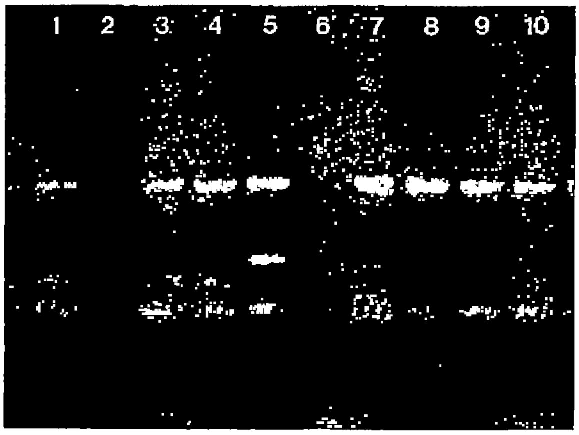

Fig. 1 K-*ras* mutation in duodenal adenomas detected by the amplification refractory mutation system. Lane 1, LS174T (positive control for Asp); lanes 3 and 4, positive for GAT mutation band of 158 base pairs; lane 5, positive for TGT mutation band of 191 base pairs; lanes 7–10, negative for K-*ras* mutation. Samples on lanes 3–5 show positive results for Asp, Asp and Cys mutations respectively

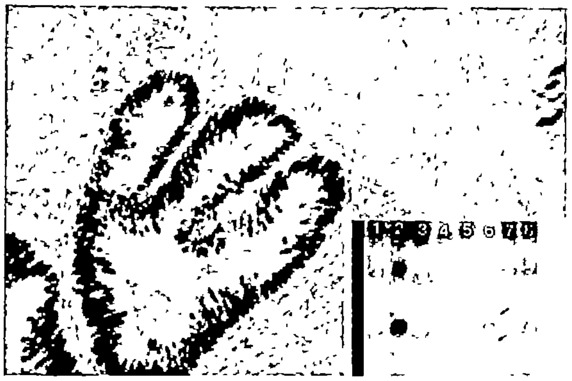

Fig. 2 *TP53* mutation in duodenal adenoma with positive p53 staining. *TP53* mutation in exon 6 was detected by polymerase chain reaction–single-strand conformation polymorphism Note two additional bands (arrowed) in lane 6

Table 1 K-*ras* and p53 status in duodenal polyps in patients with familial adenomatous polyposis

	Degree of dysplasia of the polyps		
	Non-adenomatous ($n = 7$)	Mild ($n = 23$)	Moderate ($n = 2$)
K-*ras* mutation	0	2	1
TP53 mutation	0	0	1
p53 expression	0	18	2

Discussion

Periampullary cancers account for most deaths in patients with FAP after prophylactic colectomy[2]. Detection of genetic events associated with early stages of duodenal tumorigenesis may be helpful in selecting patients at high risk of developing periampullary cancer.

Patients with FAP develop several kinds of cancer, particularly of the gastrointestinal tract[1], and so may be especially susceptible to the effect of carcinogen exposure. Because duodenal lesions cluster around the ampulla in patients with FAP[3], it is hypothesized that the bile in these patients carries carcinogens. A somatic mutation, in addition to the inherited mutation in the allele of the adenomatous polyposis coli (*APC*) genes, has been found in precancerous lesions in the FAP duodenum[17], which may indicate a carcinogen-rich environment in the duodenum. Recent evidence shows that patients with FAP may have abnormal carcinogen metabolism (e.g. glutathione *S*-transferase μ, cytochrome P450 and *N*-acetyltransferase[18]), which may also explain the increased activity of carcinogens around the ampulla of these patients. Increasing evidence for a possible carcinogen in the bile of patients with FAP supports this clinical finding; there is an abnormal profile of bile acids in these patients[19], as well as a possible carcinogenic effect of the bile on rat intestine[6] and a high level of DNA adduct formation in the FAP duodenum[5]. Thus, because patients with FAP may be particularly susceptible to carcinogen exposure and because their bile may contain an active carcinogen, it is possible that DNA damage occurs frequently in the FAP duodenum.

In colonic adenomas in patients with FAP, K-*ras* and *TP53* mutations are reported to occur in 7–25 per cent[20–23] and 3–5 per cent[24,25] respectively. The frequency of K-*ras* and *TP53* mutations found in the duodenal adenomas in this study was consistent with these results. In the present study, however, p53 overexpression was found at a strikingly high prevalence compared with the frequency of genetic mutation. Although positive p53 immunostaining often corresponds to an underlying gene mutation, much evidence of p53 overexpression without mutation has accumulated. Several kinds of cellular proteins and viruses act to stabilize p53 protein. Because wild-type p53 is upregulated in the nucleus after DNA damage[7,8,10] and the half-life of p53 protein extends after ultraviolet irradiation[26], abnormal stabilization of non-mutated p53 protein might reflect an abnormal cellular environment[27,28]. More recently it has been suggested that functional inactivation without structural mutation of p53 causes liver cancer[29]. p53 interacts with DNA replication factor[30] and plays a role in the control of DNA replication after DNA damage[28]. p53 also may help to delete damaged cells with malignant potential[31]. In cells that are allowed to pass the p53-gated checkpoint, replication of damaged DNA may follow, allowing oncogenic and/or suppressor gene mutations to occur and accumulate, contributing to neoplastic transformation. Frequent p53 overexpression in normal cells in patients from cancer families[32] supports this scenario.

It is hypothesized that the high frequency of p53 overexpression may reflect an abnormal cellular environment, particularly DNA damage, in the FAP duodenum. p53 overexpression may be a good marker for selecting patients at high risk of duodenal cancer.

Acknowledgements

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British Journal of Surgery 1997, 84, 830

Surgical workshop

Intragastric endoscopic surgery using the transanal endoscopic microsurgery technique

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A new technique is reported for intragastric endoscopic surgery that allows minimally invasive resection of intramucosal carcinoma of the stomach. This operative method is applied using the transanal endoscopic microsurgery (TEM) technique[1,2]. Intramucosal carcinomas in the posterior wall of the stomach, especially in the upper third of the stomach, remain difficult to remove by gastrofibrescopic mucosal resection[3] or laparoscopic wedge resection[4] and, therefore, these carcinomas are the best candidates for this technique.

Surgical technique

A midline incision about 4 cm long in the upper part of the abdomen is made under general anaesthesia. After entry into peritoneal cavity, an incision about 4 cm in the anterior wall of the stomach is made, and a temporary gastrostomy is performed with a series of interrupted sutures between the gastric and abdominal walls. The rectoscope[1,2] is inserted via this gastrostomy and advanced under direct vision to the desired location in the stomach, then locked by a supporting device. A video camera utilizing a glass fibre optical system transmits to a video monitor, which permits the surgical resection of gastric tumours. A carbon dioxide gas insufflation system is not used. A variety of instruments necessary for surgery can be inserted through the unsealed rectoscope, and electrical coagulation and suction are easily performed (*Fig. 1*).

A margin of clearance is marked by punctuated coagulations placed around the tumour. After injecting saline into the submucosal layer, the tumour, together with the margin of healthy mucosa, is dissected carefully and removed from the underlying circular muscle layer. After complete haemostasis, several interrupted transverse 3/0 polyglactin mucosal sutures are placed to approximate the mucosal edges. Finally, after removal of the rectoscope, the temporary gastrostomy is closed.

Two patients with intramucosal adenocarcinomas (superficial raised types, 24 × 18 mm and 20 × 18 mm in diameter) located in the posterior wall of the upper third of the stomach underwent successful mucosal resection with short operating times (104 and 98 min) and minimal blood loss (20 and 25 ml).

Discussion

Non-surgical techniques for the treatment of early gastric cancers, including endoscopic mucosal resection and laparoscopic wedge resection, have come into wide use[3,4]. However, these techniques cannot always be performed because of the location of the lesions, especially those in the posterior wall of the upper third of the stomach. Therefore, for the purpose of resecting these lesions, the TEM technique, which has emerged as a minimally invasive means of resecting rectal tumours was applied[1,2].

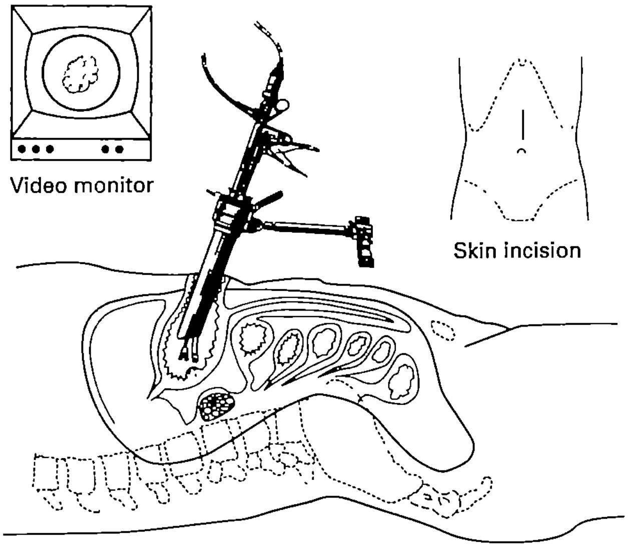

Fig. 1 Schematic view of intragastric endoscopic surgery using the transanal endoscopic microsurgery (TEM) technique. A temporary gastrostomy about 4 cm long is made, and the tube of the rectoscope is inserted via this gastrostomy. A video camera with transmission is employed Using the TEM technique, the gastric tumour is resected

In the stomach, well differentiated, intramucosal adenocarcinomas of a superficial raised lesion (diameter less than about 2 cm)[3] remain difficult to remove by endoscopic mucosal resection or laparoscopic wedge resection and are, therefore, candidates for intragastric endoscopic resection using the TEM technique. Current surgery using the TEM technique is less invasive than conventional gastrectomy. One advantage over endoscopic mucosal resection is that resection for tumours and the mucosal sutures can be performed with direct vision. Furthermore, resection can be extended to include partial or full-thickness resection of the gastric muscle layer. This surgical procedure is technically feasible and well tolerated by the patient. The authors believe this resection technique will become valuable to surgeons for application in a limited group of patients in whom other minimally invasive techniques cannot be performed.

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TUR syndrome and endoscopic transanal resection: no evidence for a clinically important association in 38 procedures

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Background The TUR syndrome is well described after transurethral resection of the prostate. Endoscopic transanal resection (ETAR) is increasingly used to remove rectal lesions.

Methods A prospective study of 38 ETARs in 21 patients was carried out over 2 years. Each patient was observed for symptoms and signs of TUR syndrome, and each had serial venous blood sampling and subsequent biochemical and haematological analysis during the perioperative period.

Results No symptoms or signs typical of TUR syndrome were recorded. However, analysis of the biochemical variables using the Kruskal–Wallis one-way analysis of variance showed that there were statistically significant ($P < 0{\cdot}05$) subclinical changes during the 24 h following the procedure affecting levels of serum sodium, potassium, total protein, albumin, lactate dehydrogenase, glycine, ammonia and serum osmolality.

Conclusion The changes in the electrolyte concentrations, although statistically significant, were not of the same magnitude as described previously in the TUR syndrome. The risk of a TUR-type syndrome in ETAR is small and serial blood tests, as detailed above, may safely be omitted.

Endoscopic transanal resection (ETAR) using a urological resectoscope and glycine irrigation is becoming a well recognized treatment of sessile rectal adenoma and some selected rectal carcinomas. It is particularly suitable for treating patients regarded as representing a poor anaesthetic risk. It is also used to excise benign lesions in patients who would otherwise require more major surgery. The sudden and unexpected death of an 85-year-old man at night 16 h after an ETAR for villous adenoma raised the possibility that he may have developed a 'TUR syndrome' and provided the impetus for the present study. The TUR syndrome is a well described clinical entity arising in the postoperative period after transurethral resection of the prostate. Absorption of large volumes of the irrigating fluid used during this urological operation can lead to cardiovascular and neurological signs and symptoms which together make up the TUR syndrome.

The physiological changes observed in the TUR syndrome are hypervolaemia, dilutional hyponatraemia, hyperglycinaemia, hyperammonaemia and hypo-osmolality[1–5]. These changes individually or in combination cause cerebral oedema and encephalopathy. More recently the cardiovascular and central nervous system symptoms associated with the syndrome and the biochemical changes have also been described in gynaecological patients undergoing transcervical endometrial resection[6,7].

ETAR using a urological resectoscope has been advocated in the management of rectal lesions below the peritoneal reflexion and too high comfortably to be removed through the peranal route by 'open' surgery[8–10]. The ETAR technique involves irrigating the rectum with 1·5 per cent glycine solution. A prospective study was undertaken to record any perioperative signs and symptoms associated with a TUR-type syndrome, and to measure the absorption of the glycine together with any electrolyte disturbances.

Patients and methods

Over a 2-year period 38 procedures performed on 21 patients for rectal adenoma and rectal carcinoma were evaluated.

The technique has been described previously[8]. The rectum is prepared by the administration of two rectal washouts the evening before surgery. Antibiotic prophylaxis using cefuroxime 750 mg and metronidazole 500 mg is given intravenously on induction of anaesthesia. A standard 24-Fr urological resectoscope (Karl Stortz Endoscopes, Rimmer Brothers, London, UK) with a 30° telescope is inserted through the anus, and resection is carried out using the loop cutting electrode with 1·5 per cent glycine as the irrigant. After the procedure a 28-Fr Foley catheter is placed into the rectum.

Each patient had a series of venous blood samples taken during the perioperative period. The pulse rate and mean arterial pressure were recorded on taking each sample. The first (preoperative) sample was taken in the anaesthetic room, and subsequent samples were taken after 10, 20 and 30 min and 4 and 24 h after the start of glycine irrigation. The concentrations of sodium, potassium, urea, creatinine, total protein, albumin, lactate dehydrogenase and haemoglobin together with osmolality and haematocrit were measured by standard techniques on each sample. Glycine levels were measured using a Hilger Chromospek (Rank–Hilger, UK) amino acid analyser with ninhydrin detection, and ammonia levels were measured using a Sigma Diagnostics (Poole, UK) analyser.

Careful documentation of the total volumes of 1·5 per cent glycine infused and collected was made, as well as the duration of the procedure. Also recorded were the weight of resected tumour, the estimated blood loss and the volume of fluid in the rectal tube at 24 h. All patients were observed carefully at operation for any changes in pulse rate and blood pressure. Also recorded were any symptoms of nausea, vomiting, headache, visual disturbance, agitation, confusion and lethargy.

All data were entered into a computerized database, and the median value and interquartile range (i.q.r.) for each variable at each time interval was calculated. The median values for each variable at each of the six different time intervals were then compared using the Kruskal–Wallis one-way analysis of variance.

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Results

The median age of the patients was 69 (range 51–86) years, the median length of the procedure 16 (i.q.r. 10–23·5) min and the median weight of resected tumour was 6·5 (i.q.r. 5·0–20·0)g.

The median volume of glycine used was 4050 (i.q.r. 2000–6700) ml. The net glycine median volume, the difference between the irrigant volume infused and the volume recovered, was 750 (i.q.r. 338–1350) ml, and the median volume of fluid in the rectal tube at 24 h was 100 (i.q.r. 50–300) ml.

There was no significant difference in pulse rate and mean arterial pressure during the 24-h period. One patient suffered considerable postoperative bleeding which required a return to theatre and a 4-unit blood transfusion. Two further patients suffered rigors approximately 4 h after the procedure; both recovered rapidly with further antibiotic treatment and subsequently were found to have positive blood cultures. A female patient who suffered from senile dementia became 'more confused' during the first 48 h, but recovered to her preoperative state by the time of discharge. These four patients apart, there were no other complications or symptoms that could be attributed to a TUR-type syndrome. No procedure was complicated by rectal perforation.

A review of the histology of the chippings confirmed that the deep edge of the resection crossed just into the muscle layer for the benign tumours in a way that parallels the observations on resection margins in superficial bladder tumours; no such observations were possible to suggest depth of resection in the carcinomas.

The median (i.q.r.) values for each variable at each time interval are shown in *Table 1*. The following variables showed statistically significant changes in concentration over the 24-h period ($P<0.05$): osmolality ($P<0.023$), lactate dehydrogenase ($P<0.037$), sodium ($P<0.001$), potassium ($P<0.043$), total protein ($P<0.002$), albumin ($P<0.001$), glycine ($P<0.024$) and ammonia ($P<0.014$). The median values for glycine and ammonia at each time point are plotted in *Fig. 1*.

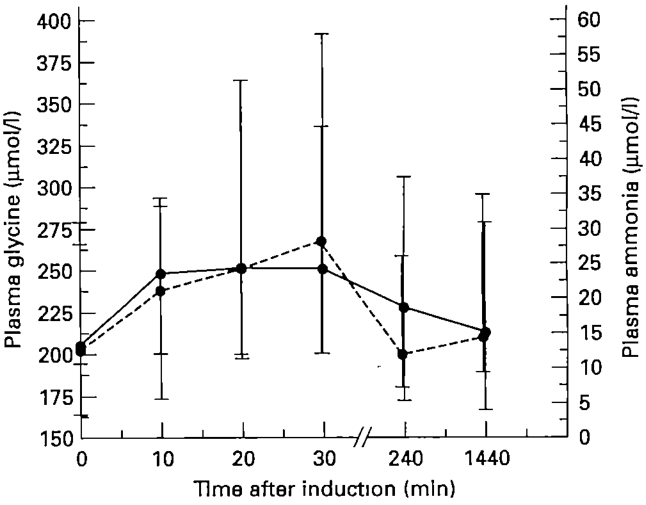

Fig. 1 Changes in ammonia (---) and glycine (———) concentrations following induction of anaesthesia. Values are median (interquartile range)

Table 1 Biochemical and haematological analysis

	Time after induction of anaesthesia					
Variable	0	10 min	20 min	30 min	4 h	24 h
Pulse (beats per min)	76 (72–82)	73 (64–80)	70 (64–80)	74 (63–80)	76 (69–84)	76 (70–80)
MAP (mmHg)	95 (87–104)	90 (79–100)	90 (80–101)	90 (82–101)	92 (87–102)	93 (86–102)
Haemoglobin (g/dl)	13·2 (11·8–14·2)	12·6 (11·0–13·8)	12·5 (10·9–13·7)	12·6 (10·8–13·5)	12·9 (11·4–13·8)	12·6 (11·3–13·7)
Haematocrit	0·393 (0·352–0·418)	0·371 (0·332–0·402)	0·378 (0·328–0·398)	0·369 (0·323–0·397)	0·380 (0·336–0·409)	0·374 (0·342–0·400)
Sodium (mmol/l)	138 (137–140)	138 (137–139)	138 (137–139)	139 (137–140)	138 (137–139)	136 (136–138)
Potassium (mmol/l)	4·0 (3·7–4·1)	3·7 (3·6–3·9)	3·7 (3·4–3·9)	3·7 (3·5–4·0)	3·8 (3·7–4·1)	3·9 (3·7–4·0)
Urea (mmol/l)	5·0 (3·9–5·7)	4·6 (3·8–5·7)	4·8 (3·9–5·5)	4·7 (3·8–5·4)	4·5 (3·6–5·4)	4·6 (3·9–5·8)
Creatinine (µmol/l)	85 (77–98)	78 (72–96)	78 (70–95)	81 (72–96)	81 (71–96)	88 (80–104)
Total protein (g/l)	72 (68–78)	67 (63–72)	68 (63–71)	66 (63–70)	66 (63–73)	70 (64–76)
Albumin (g/l)	40 (37–42)	36 (34–39)	36 (34–38)	36 (34–38)	37 (34–39)	38 (35–40)
LDH (units/l)	495 (431–550)	450 (373–498)	406 (356–502)	436 (379–573)	446 (396–514)	436 (385–503)
Glycine (µmol/l)	206 (163–278)	248 (174–287)	252 (198–363)	251 (201–392)	229 (172–305)	214 (167–278)
Ammonia (µmol/l)	12 (10–28)	21 (12–34)	24 (12–51)	28 (12–44)	12 (7–26)	14 (10–34)
Osmolality (mosmol/kg)	292 (289–295)	290 (286–294)	290 (285–294)	290 (286–293)	288 (284–293)	287 (282–292)

Values are median (interquartile range) MAP, mean arterial pressure; LDH, lactate dehydrogenase

Discussion

For many years hyponatraemia complicating transurethral prostatic resection has been recognized as a contributory factor to the symptoms and signs associated with the TUR syndrome[1]. In more recent times it has been proposed that the symptoms may be a result of an accumulation of glycine and its breakdown products, glycolic acid and glyoxylic acid[4], hyperammonaemia[2,3], together with hypo-osmolality[11] or a combination of all four. In large series of transurethral prostatectomies the incidence of the TUR syndrome has been quoted at 2 per cent[12]. Symptoms of the syndrome may occur when serum sodium concentration falls below 135 mmol/l, but most clinical reactions occur when the serum sodium has fallen by 15–20 mmol/l. A level of 120 mmol/l or less is regarded as the point distinguishing moderate from severe reactions[3]. This study has shown a statistically significant fall in serum sodium concentration in patients undergoing ETAR but only of 1·5 mmol/l. There were also statistically significant rises in serum ammonia and glycine levels. The rise in ammonia in individual patients was up to three times the upper limit of normal, but a level of ten times the upper limit of normal occurs in patients who develop the TUR syndrome[3].

The most likely reason for the smaller changes in the above electrolyte concentration in ETAR compared with transurethral resection of prostate (TURP) is the relatively shorter duration of the procedure and consequently the smaller quantity of 1·5 per cent glycine irrigant absorbed (median 16 min and 750 ml respectively in this study). The absorption of 1 litre of 1·5 per cent glycine or more in TURP is generally accepted as a level above which patients become at significant risk of developing the syndrome[13]. It also seems possible that the rectum may have a lesser tendency than the highly vascular prostatic bed to absorb irrigant during resection, and of course the rectum is not irrigated in the immediate postoperative period. Significant changes in glycine and ammonia concentrations during ETAR have been described previously in a small series (nine patients), particularly in one case complicated by rectal perforation[14]. However, these were not accompanied by significant changes in the serum osmolality and sodium concentration[14]. The changes in total protein and albumin levels in this study are in keeping with a mild subclinical TUR syndrome.

In conclusion the risk of a TUR-type syndrome in patients undergoing ETAR appears to be small, although it cannot be entirely dismissed by a study of this size and further investigation, particularly of patients who have undergone long or complicated procedures, may be necessary. Thus it is concluded that routine intensive blood testing as detailed above is unnecessary in uncomplicated ETAR, and should be omitted. A simple estimation of the haematocrit and urea and electrolyte concentrations is quite sufficient.

Acknowledgements

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Detection of circulating tumour cells and nodal metastasis by reverse transcriptase–polymerase chain reaction technique

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Background In the search for occult metastases in lymph nodes or circulating tumour cells, a reverse transcriptase–polymerase chain reaction (RT-PCR) assay was developed to detect tumour-specific splice variants of the transcript of the CD44 gene. The assay was highly sensitive and could detect ten tumour cell per 10^6 leucocytes.

Methods RNA was purified from peripheral blood ($n = 24$) and regional lymph nodes ($n = 14$) from patients with colorectal cancer. Complementary DNA was made and amplified using primers specific for the CD44 gene. Southern blotting with exon-specific probes was used to enhance the sensitivity.

Results Tumour cells were detected in peripheral blood samples in four patients and lymph nodes in nine, in one of whom conventional histology had not detected tumour cells.

Conclusion This technique may be useful in the early diagnosis of primary or metastatic tumours, in assessing prognosis and in detecting residual disease after treatment.

Micrometastatic tumour cells in blood or lymph nodes produce no clinical symptoms when present as single cells or microaggregates and cannot be detected by current imaging techniques. The detection of these rare cells requires a novel sensitive technique of detection.

Historically, conventional cytology has been the main method for the detection of circulating tumour cells and lymph node metastasis. However, this method can detect tumour cells only at a level of one in 100 normal cells and is notoriously inaccurate[1]. Immunocytochemistry, although more sensitive (detecting one cell per 10^5 normal cells[2]), is dependent on the availability of antibodies to tumour-associated cell surface antigens, and may be subject to false-positive results when antibodies cross-react with host immune cell antigens.

With the advent of the reverse transcriptase–polymerase chain reaction (RT-PCR) to amplify tumour-specific RNA sequences, the detection of very rare tumour cells (one tumour cell in 10^7 normal cells) becomes feasible[3–5]. In this, the choice of target RNA is crucial. It must obviously be readily distinguishable from RNA in normal cells, or at least not expressed in normal cells in the tissues that are being tested for the presence of tumour cells. For example, the neuroendocrine gene PGP 9.5 is not expressed by leucocytes and so detection of its messenger RNA (mRNA) in blood is good evidence for the presence of neuroblastoma cells in the blood[4].

A potentially valuable tumour cell marker is CD44. The gene encoding CD44 protein is found on chromosome 11p and comprises 20 exons spanning 50 kilobases. The CD44 protein exists as multiple isoforms generated by 'alternative splicing'[6], a mechanism that allows cells to exclude and include specific segments of mRNA in the final transcript, thereby generating a family of related proteins from a single gene. At least ten of the exons are involved in the alternative splicing pathways[7]. The standard form, CD44S, lacking all ten variable exons, is expressed mainly on cells of haematopoietic and mesodermal origin[8]. In contrast, the distribution of other more complex variant isoforms (CD44v), which contain multiple alternative spliced exons, is found predominantly in tumour cells[7–9].

Recent studies of CD44 gene activity in colorectal cancer[10] have confirmed that there is chaotic overexpression of many abnormal and unusual mRNA transcripts in all tumour samples, relative to samples from corresponding normal tissues[11,12]. The strong association between altered CD44 expression and malignancy means that this mRNA marker can be used to detect tumour cells in tissues or body fluids such as blood, urine or peritoneal fluid. Matsumura *et al.*[13] have recently used this RT–PCR technique to detect exfoliated cancer cells in the urine of patients with early bladder cancer[13]. No study has yet used this technique to detect circulating tumour cells and occult nodal metastases in colorectal cancer. In this study, a sensitive assay was sought for the detection of circulating tumour cells and nodal metastases using CD44 splice variants as a tumour marker.

Patients and methods

The entire CD44 gene assay consisted of five steps: (1) density gradient centrifugation of nucleated cells; (2) total RNA extraction; (3) CD44 RT–PCR of total RNA; (4) agarose gel electrophoresis of PCR products; and (5) blot hybridization with CD44S, variant 2 (V2) and variant 7 (V7) probes.

Patient blood specimens

Twenty-four patients with colorectal cancer were studied to determine whether tumour cells could be detected in the peripheral blood. Sixteen patients were male and eight female; their median age was 70 (range 50–88) years (*Table 1*). Three patients undergoing abdominal surgery for benign disease and eight healthy volunteers were recruited as controls, seven men and four women of median age 47 years.

Approximately 15 ml venous blood was obtained from the antecubital vein without tourniquet using ethylenediamine tetra-acetic acid tubes. Whole blood was mixed with an equal volume of RPMI medium (Gibco-BRL, Paisely, UK) which was then

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Table 1 Clinical pathological details of patients from whom peripheral blood was taken, with respect to site and stage of tumour

Patient no.	Age (years)	Sex	Dukes stage	Tumour differentiation	Site of tumour	Operation
1	70	M	'D'	Moderate	Rectum	Anterior resection
2	71	M	B	Moderate	Rectum	Anterior resection
3	88	F	B	Well	Caecum	Right hemicolectomy
4	67	M	B	Moderate	Rectum	Anterior resection
5	54	F	C	Moderate	Rectum	Anterior resection
6*	56	M	C	Moderate	Descending	Inoperable
7	66	M	'D'	Moderate	Caecum	Right hemicolectomy
8*	75	F	'D'	Moderate	Rectum	Anterior resection
9	78	M	B	Moderate	Caecum	Right hemicolectomy
10*	74	M	'D'	Moderate	Rectum	Irresectable
11*	76	F	B	Poor	Caecum	Right hemicolectomy
12	63	M	B	Well	Rectum	Anterior resection
13	79	M	C	Well	Caecum	Right hemicolectomy
14	76	F	B	Poor	Caecum	Right hemicolectomy
15	50	M	C	Poor	Caecum	Right hemicolectomy
16	66	M	'D'	Moderate	Caecum	Right hemicolectomy
17	80	M	B	Moderate	Rectum	Anterior resection
18	80	F	B	Moderate	Rectum	Anterior resection
19	50	M	C	Poor	Transverse	Right hemicolectomy
20	52	F	'D'	Moderate	Rectum	Anterior resection
21	82	F	C	Well	Sigmoid	Sigmoid colectomy
22	88	M	C	Poor	Caecum	Right hemicolectomy
23	63	M	B	Well	Rectum	Anterior resection
24	66	M	'D'	Moderate	Rectum	Anterior resection

*Patients with circulating tumour cells detected by reverse transcriptase–polymerase chain reaction

Table 2 Clinical pathological details of patients from whom lymph nodes were harvested, with respect to site and stage of tumour

Patient no.	Age (years)	Sex	Site of tumour	Dukes stage	Operation
1	82	F	Sigmoid	C	Sigmoid colectomy
2	58	M	Transverse	B	Right hemicolectomy
3	68	M	Caecum	D	Right hemicolectomy
4	76	F	Caecum	B (C)	Right hemicolectomy
5	88	M	Caecum	B	Right hemicolectomy
6	75	M	Rectum	C	Anterior resection
7	71	M	Rectum	B	Anterior resection
8	74	F	Rectum	C	Anterior resection
9	88	M	Caecum	B	Right hemicolectomy
10	79	M	Caecum	B	Right hemicolectomy
11	73	M	Caecum	C	Right hemicolectomy
12	73	M	Caecum	C	Right hemicolectomy
13	73	F	Caecum	C	Right hemicolectomy
14	78	F	Caecum	C	Right hemicolectomy

*Lymph node sample showed deranged CD44 gene activity suggesting the presence of metastatic cells and as a result the Dukes stage changed from B to C

layered over 15 ml Lymphoprep (Nycomed Pharma, Oslo, Norway). The gradient was centrifuged at 580*g* for 20 min. The lymphocyte and granulocyte layer was carefully aspirated and rediluted with 10 ml RPMI medium in a 20-ml tube, which was then concentrated by further centrifugation at 400*g*. The supernatant was discarded, and the pellet containing nucleated cells was used for RNA extraction with Ultraspec RNA (Biotecx, Franklin, Massachusetts, USA). This commercially available preparation is used to extract total RNA based on a modification of the guanidinium thiocyanate method[14].

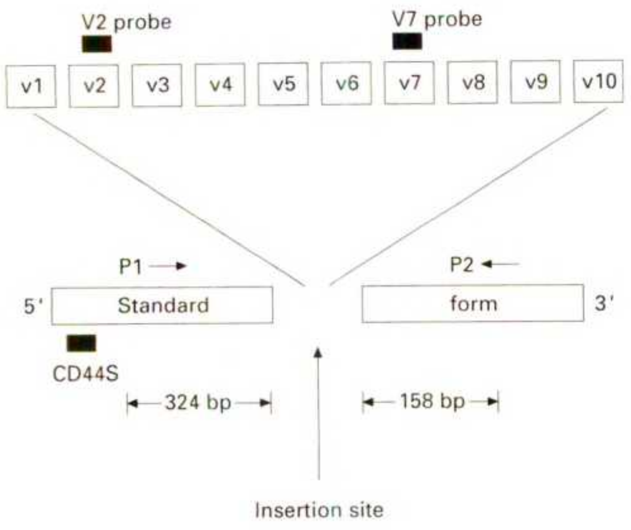
Patient lymph node specimens

Fourteen consecutive patients undergoing resection for colorectal cancer were studied of whom nine were men and five women; their median age was 74 (range 58–88) years (*Table 2*). Lymph nodes were freshly harvested from the resected specimen and divided into two equal portions, one for conventional histological staining and the other snap-frozen in liquid nitrogen and kept at −70°C until further use. Three patients with inflammatory bowel disease were also studied and their lymph nodes were harvested from the resected specimen. RNA was extracted from the lymph nodes using the above RNA extraction method.

Reverse transcriptase–polymerase chain reaction

The concentration of RNA and its purity was measured at wavelengths of 260 and 280 nm using a Shimadzu spectrometer (UV-160A; Shimadzu, Tokyo, Japan). Complementary DNA (cDNA) was synthesized from 5 µg total RNA in a 20-µl reaction mixture containing reverse transcriptase buffer (Tris 500 mmol/l, pH 8·3, potassium chloride 500 mmol/l, magnesium chloride 80 mmol/l, dithiothreitol 100 mmol/l), 10 units RNAsin ribonuclease inhibitor (Promega, Southampton, UK), oligo(dT)$_{15}$ primer 25 µmol/l (Promega), 2 mmol/l each of 2′-deoxyguanosine 5′-triphosphate, 2′-deoxycytidine 5′-triphosphate, 2′-deoxythymidine 5′-triphosphate and 2′-deoxyadenosine 5′-triphosphate 2 mmol/l (Pharmacia, Uppsala, Sweden) and 150 units Moloney leukaemia virus reverse transcriptase (Gibco-BRL). Each RNA sample was heated up to 75°C for 5 min before cooling and adding 10 µl of the above mixture. The mixture in a final volume of 20 µl was incubated at 37°C for 60 min, heated to 95°C to denature the reverse transcriptase enzyme for 5 min, and then chilled on ice. Controls with no reverse transcriptase in the mixture were also included in the reactions.

Some 5 µl cDNA was then specifically amplified using primers P1 and P4 (primer sequences are given in *Fig. 1*), designed to anneal to the CD44 sequence by a Taq polymerase (Gibco-BRL) in a volume of 50 µl, using the buffer conditions recommended by the manufacturer. Amplification was performed for 30 cycles (94°C for 1 min, 56°C for 1 min 30 s, and 72°C for 1 min). A negative control, with no template, was run with every batch.



Primers

P1 = 5' GACACATATTGCTTCAATGCTTCAGC

P2 = 5' GATGCCAAGATGATCAGCCATTCTGGAAT

Fig. 1 Schematic representation of CD44 messenger RNA (mRNA) transcript. The primers P1 and P4 flank the insertion site at which variant v1–v10 can be included in the mRNA transcript. The standard CD44 mRNA transcript lacks v1–v10 and will result in a 482 base pairs reverse transcriptase–polymerase chain reaction (RT–PCR) product. Transcript containing one or more of the variant exons will give rise to larger RT–PCR products. Probes V2 and V7 will detect only those products harbouring the corresponding exon sequence

Gel electrophoresis and Southern blot hybridization

Some $20\,\mu l$ PCR products were electrophoresed in a 1·2 per cent agarose gel and transferred to Hybond-N + nylon membrane (Amersham, High Wycombe, UK) for hybridization separately with CD44S, V2 and V7 probes (courtesy of Dr D. Tarin, John Radcliffe Hospital, Oxford) using the enhanced chemiluminescence method (Amersham). Blotting and probe labelling were performed according to the manufacturer's instructions. Filters were exposed to medical X-ray film (Fuji, Tokyo, Japan) for 5–60 min.

Reconstitution experiments

Cell-spiking experiments were used to test the sensitivity of this technique for the detection of colorectal cells in blood. Some 20 ml peripheral blood was obtained from healthy volunteers after density gradient centrifugation using lymphoprep. The suspension was pelleted by further centrifugation. The cell pellet was divided into four aliquots which were seeded with 1, 10 and $100\,\mu l$ of a suspension of 10 000 cells per ml of HCT116 colorectal cancer cell line. The HCT116 cells were cultured in Dulbecco's modified Eagle's medium plus 5 per cent fetal calf serum. An unspiked blood sample was included as a negative control. RNA was extracted from the samples and resuspended in $20\,\mu l$ diethyl pyrocarbonate-treated water. cDNA synthesis was carried out on $5\,\mu l$ RNA in each of the samples in $20\,\mu l$ reaction mixture. PCR reactions were carried out on the samples with primers P1 and P4 in similar conditions as described above. Southern blotting using CD44S probe and exon V7 and V2 were performed to increase the sensitivity of detection.

Restriction enzyme analysis

The PCR products of CD44S (482 base pairs (bp)) were purified from a 1·2 per cent agarose gel using the QIAquick Gel Extraction Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Restriction enzymes and the predicted sizes of the digested products for CD44S were obtained from the published sequence of clone 4.01 using the GCG programme and are listed in *Table 3*.

Table 3 Restriction enzyme analysis and the products of the digested fragments

Restriction enzymes	CD44S (482)
FOK I	229, 253
RSA I	45, 215, 222

All enzymes were obtained from Gibco-BRL

Results

Polymerase chain reaction primers and probes

Fig. 1 shows a schematic representation of the CD44 gene and primers. The primers are similar to those used by Matsumura *et al.*[13] and were selected to flank the insertion site at which variable exons (v1–v10) can be inserted in the mRNA transcript to produce different forms of CD44. P1 has its origin 324 bp upstream from the insertion site and P4 is 158 bp downstream. If a sample contains CD44 standard form (lacking variant exons), it would be expected to exhibit a PCR product of 482 bp. Samples containing alternative spliced variants (containing one or more variant exons) would be expected to exhibit larger amplification products, up to a maximum of 1650 bp. The probe S1 will detect all isoforms, whereas V7 and V2 probes will detect only those harbouring the corresponding exons.

Patient blood analysis

Following RT–PCR of CD44 mRNA from patients' peripheral blood, a single band of 482 bp corresponding to the CD44S form was identified by gel electrophoresis (*Fig. 2*). However, some of the amplified products were at too low a concentration to be visible by gel electro-

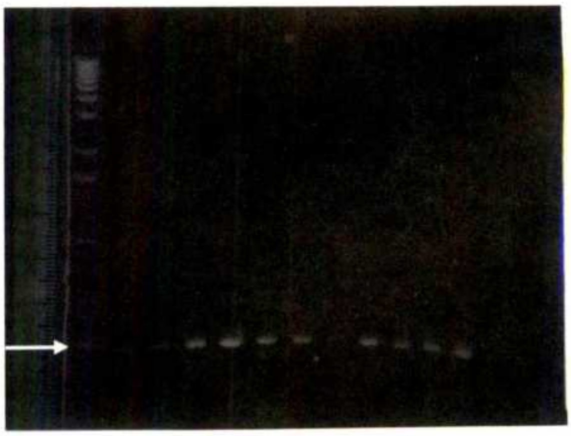


Fig. 2 Gel electrophoresis of reverse transcriptase–polymerase chain reaction samples from the blood of patients with colonic cancer. Many of the amplified PCR products resolved by electrophoresis were invisible in gel. The CD44S (arrow) is easily recognizable

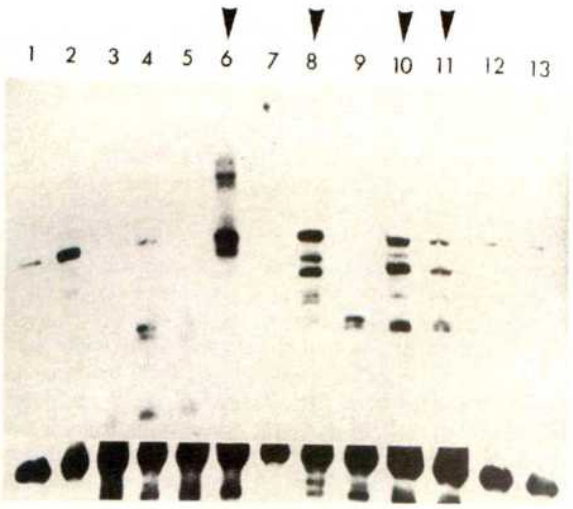


Fig. 3 Autoradiographs of reverse transcriptase–polymerase chain reaction products from the peripheral blood of patients with colonic cancer after hybridization with V7 (upper panel) and CD44S (lower panel) probes. All samples showed bands of 482 base pairs, the standard form of the CD44 transcript with the CD44S probe. Deranged CD44 gene activity was seen in blood from patients 6, 8, 10 and 11, suggesting the presence of circulating tumour cells. Bands that were invisible in the gel in *Fig. 2* appeared in the blot after exon-specific blotting

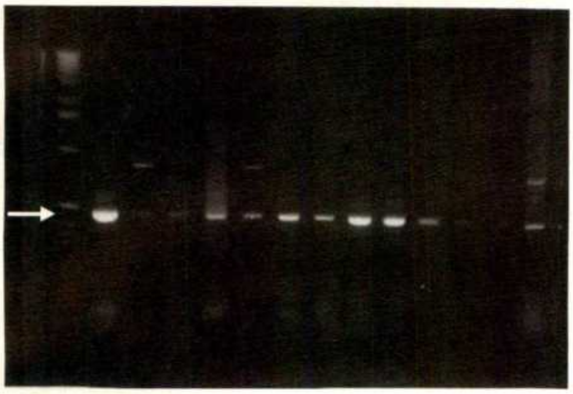


Fig. 4 Gel electrophoresis of reverse transcriptase–polymerase chain reaction samples from the lymph nodes of patients with colonic cancer. Many of the CD44 splice variants are not easily visible by gel electrophoresis. Lanes 2 and 4 were lymph nodes with metastatic deposits as confirmed by conventional histology in patients with Dukes C carcinoma. Lane 13 was from a liver secondary in a patient with Dukes 'D' carcinoma of the colon. The CD44S (arrow) is easily recognizable

phoresis. To increase further the sensitivity of the detection, Southern blotting using CD44S, V2 and V7 was performed. Bands that were invisible in the gel appeared in the blot after exon-specific blotting (*Fig. 3*). Of the 24 blood samples, four showed abnormal CD44 gene activity in the peripheral blood, indicating the presence of circulating tumour cells. In the case of controls, all samples showed CD44S, with no overexpression of CD44 variants (results not shown).

Lymph nodes

Gel electrophoresis (*Fig. 4*) followed by blot hybridization (*Fig. 5*) was used to detect CD44 gene activity in the

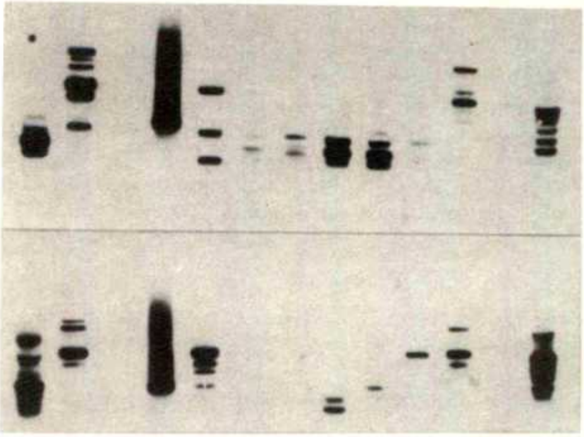


Fig. 5 Southern blotting was carried out on the gel in *Fig. 4*. Autoradiographs of reverse transcriptase–polymerase chain reaction products of the lymph nodes after hybridization with the V2 (upper panel) and V7 (lower panel) probes showed that the metastatic deposits in lymph nodes overexpressed several splice variants compared with normal lymph nodes. Bands that were invisible in the gel in *Fig. 4* appeared in the blot after exon-specific blotting

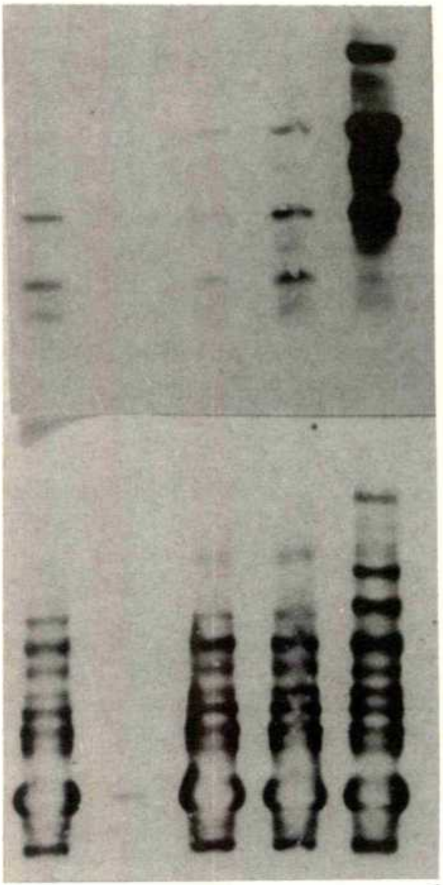


Fig. 6 Autoradiograph of polymerase chain reaction products of peripheral blood seeded with known numbers of HCT116 colorectal carcinoma cell lines after hybridization with the V2 (upper panel) and CD44S (lower panel) probes. The technique could detect tumour cells down to a concentration of ten tumour cells in a sample of 10^6 leucocytes

lymph node samples. Nine patients had lymph node metastases detected by conventional histology and RT–PCR CD44 gene assay. Moreover, in one case where conventional staining failed to detect any tumour cells in the regional nodes, RT–PCR was able to demonstrate their presence in the samples. Therefore, in this patient, the failure to detect occult nodal metastasis had resulted in falsely optimistic tumour staging.

Calibration of sensitivity

In tumour cell-spiking experiments, it was possible to detect ten tumour cells per 10^6 peripheral blood lymphocytes (*Fig. 6*). The normal blood did not show overexpression of the CD44 splice variant.

Confirmation of reverse transcriptase-polymerase chain reaction product

Restriction enzyme analysis of the CD44 products confirmed that the amplified fragments were specific for CD44, as seen in *Table 3*.

Discussion

Local recurrence and metastasis continue to pose major problems in the clinical management of patients with colorectal cancer. The presence of metastatic deposits in the regional lymph nodes is of major prognostic significance[15], but the significance of tumour cells in the circulation is less clear in patients with colorectal cancer. Little is known about the relationship between circulating tumour cells and the development of secondary disease, except that the process of implantation of tumour cells from peripheral blood is inefficient because fewer than 0·1 per cent of circulating tumour cells survive in the circulation[16]. However, the continued presence of circulating tumour cells is likely to result in a poor prognosis. Therefore, the detection of circulating tumour cells may be an aid to decisions regarding therapy.

A highly sensitive reverse transcription assay capable of detecting occult nodal metastasis and circulating tumour cells in patients with colorectal cancer was developed. In contrast to tissue-specific transcripts such as cytokeratin previously used in detecting circulating tumour cells[17], this method relies on the detection of abnormal alternatively spliced CD44 mRNA transcripts, thus ensuring optimal specificity. In previous studies[10,11], the present authors and others have shown that there is a strong association between overexpression of the CD44 splice variants and the presence of malignant cells within a sample. The differences in the CD44v expression between normal and cancer tissue observed with RT–PCR could, in theory, be due to the increased number of inflammatory cells present within the tumour samples. However, this theory was refuted by Gorham and colleagues[18] in a recent study using *in situ* hybridization analysis of variant (CD44) mRNA in cryostat sections of normal and neoplastic colonic mucosa with ^{35}S-labelled riboprobes. They showed that CD44V mRNA levels are raised specifically in regions of malignant cells but not in inflammatory cells, confirming observations seen with other techniques including RT–PCR[10,11] and immunohistochemistry[19] that CD44 gene activity is increased in malignancy. Therefore, it is reasonable to infer from this study that overexpression of abnormal CD44 splice variants in a tissue or blood sample is highly suggestive of the presence of cancer cells.

RT–PCR followed by blot hybridization with exon-specific probes is an extremely sensitive way of analysing CD44 complex alternative splicing compared, for example, with Northern blotting, which requires a large amount of RNA. Larger volumes of blood would be required than are practical for diagnostic purposes. This cDNA–PCR–blot hybridization technique would be able to detect small amounts of abnormal and unusual transcripts. Using this unique approach, not only could a series of blood samples and lymph nodes be examined rapidly, but the analysis of small amounts of biological materials was shown to provide information of clinical interest. Its sensitivity, assessed by means of reconstitution experiments, is more than one cell per 10^6 leucocytes.

The major drawback of this method are the numerous steps needed to process from collection to final purification of RNAs. An error occurring during any of these steps may result in degraded RNAs, giving rise to false-negative results. The other major drawback is cross-contamination linked to the use of PCR amplification techniques. Such contamination may generate false-positive results. The other disadvantage is that the technique necessitates the destruction of tissues and cells using guanidinium to extract RNA and therefore it is not possible to determine the cellular distribution of the CD44 gene transcripts within a tumour sample. Lastly, enumerating circulating tumour cells with this technique requires semiquantitative RT–PCR, which is technically demanding. However, the technique is potentially useful in confirming the absence of tumour cells in lymph nodes.

The use of the RT–PCR CD44 gene assay to detect tumour cells in the circulation or lymph nodes is likely to provide an important predictive tool with respect to recurrence and metastasis and to result in earlier selection of patients for adjuvant therapy.

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Surgical workshop

Long-term expandable stent as a definitive treatment for benign rectal stenosis

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Rectal stenosis is a relatively common complication of colorectal cancer, rectal surgery, radiation therapy or inflammatory disease. Other causes of benign rectal stricture are less common[1] and can be treated without resection using endoscopic and other modalities[2,3].

Expandable stents have been used successfully in the temporary treatment of neoplastic obstruction and palliatively when surgery cannot be performed[4,5]. The use of an expandable stent as definitive treatment for benign rectal stenosis is described.

Surgical technique

Under radiological control (*Fig. 1a*), after dilatation with an 8-mm balloon catheter (Boston Scientific, Watertown, Massachusetts, USA) (*Fig. 1b*), a self-expanding Wallstent of 70 mm in length and 22 mm in diameter (Schneider, Bulach, Switzerland) was placed across the stenosis, 2 cm above and below the stricture to avoid undesirable movements of the stent. The stent was inserted over a 'super-stiff' guidewire (0·035 inch; Cook Europe, Bjaeverskov, Denmark), introduced anally through a 7-Fr Berenstein catheter (C. R. Bard, Billerica, Massachusetts, USA). Subsequent dilatation with a 20-mm balloon catheter resulted in complete expansion of the stent (*Fig. 1c*). The procedure was performed on an outpatient basis.

Paraffin oil 5 ml orally per 8 h was given, and cleaning enemas were administered with a rectal probe through the rectal stent at monthly intervals.

Clinical details

A 71-year-old man presented with a rectosigmoid stenosis 10 mm long with a lumen of 3 mm in diameter. Endoscopy revealed a constricting lesion 8 cm from the anal margin and distal progression was not possible. Histological examination of multiple biopsies, including full rectal wall biopsy, revealed granulation tissue only. There was no evidence of Crohn's disease.

Balloon dilatation and transanal staple gun resection (under spinal anaesthesia) were tried initially without success because the stricture was very rigid.

The patient tolerated placement of the stent well and without complication. During the first year of follow-up three episodes of faecal impaction were treated successfully by passing a rectal probe through the stent, and oral laxative therapy. The patient noted anal discomfort during defaecation and needed laxative therapy to achieve a normal stool. One-year follow-up showed that the stent remained fully expanded (*Fig. 2*).

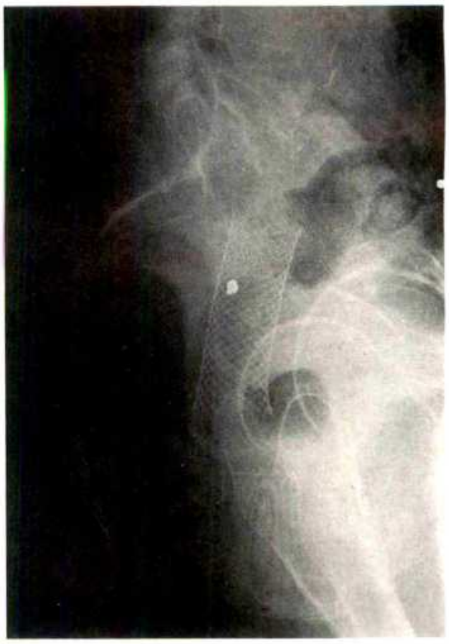
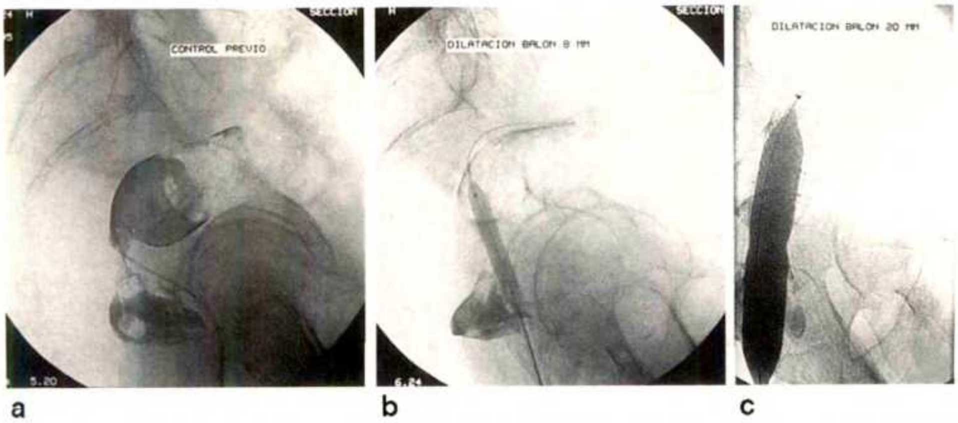


Fig. 2 Radiograph at 1-year follow-up shows that the stent has remained fully expanded



a **b** **c**

Fig. 1 Placement of the expandable stent. **a** Site of the stenosis under radiological control; **b** dilatation with an 8-mm balloon; and **c** dilatation with a 20-mm balloon and complete expansion of the stent

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Discussion

An expandable stent provides a new method of treatment of colorectal strictures of different aetiology. Such stents have been used successfully for temporary or palliative treatment of neoplastic colorectal obstructions[4,5].

Application of expandable stents to benign colorectal stricture provides a rapid, straightforward and effective method of treatment.

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Randomized controlled trial with sequential design of laparoscopic *versus* conventional appendicectomy

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Background A prospective study including 272 patients with suspected appendicitis was performed. The aims were to evaluate the representativity of the study group and to compare diagnostic and therapeutic laparoscopy with conventional appendicectomy.

Methods The study was an open, randomized, single-centre trial with sequential design. One hundred and eight patients were randomized between laparoscopy or conventional appendicectomy, of whom 84 had acute appendicitis. Duration of postoperative convalescence was the major endpoint.

Results The study patients were representative of the eligible population regarding age and stage of appendicitis. The risk of unnecessary appendicectomy was significantly ($P = 0{\cdot}03$) lower after laparoscopy. The mean difference in duration of postoperative convalescence was 4·7 days in favour of laparoscopic appendicectomy ($P = 0{\cdot}07$), and 26 min in duration of operation in favour of conventional appendicectomy ($P < 0{\cdot}01$). No differences were detected in postoperative hospital stay, pain assessment or complications.

Conclusion The laparoscopic procedure is at least as good as conventional appendicectomy. Initial laparoscopy reduces the rate of misdiagnosis.

Appendicectomy is one of the most common minor abdominal operations, and can safely be performed laparoscopically[1–14]. The evidence from randomized[1–6] and non-randomized[7–14] studies tends to favour laparoscopic appendicectomy. Two randomized series[15,16] concluded that diagnostic laparoscopy reduced the risk of unnecessary appendicectomy in women. In a prospective, non-randomized study[10] laparoscopic appendicectomy was found superior with regard to duration of postoperative hospital stay, postoperative convalescence and rate of unnecessary appendicectomy. However, conventional appendicectomy had a shorter operation time and lower risk of minor complications. Non-randomized studies might have pitfalls which alter the conclusions.

To compare conventional and laparoscopic appendicectomy, randomized clinical trials (RCTs) are needed. However, because of the selection criteria, and for administrative and practical reasons, the study population in a RCT is usually only a fraction of the actual patient population[1–6,17–19]. This might affect the validity of the conclusions, but is rarely reported or discussed. The aims of the present paper were to evaluate the representativity of the study population, to evaluate laparoscopy in patients with suspected appendicitis and to compare laparoscopic and conventional appendicectomy in patients with proven acute appendicitis.

Patients and methods

Patients

The total study group included 136 women and 136 men (*Fig. 1*) with a mean age of 33 (range 4–86) years. The patients underwent operation between October 1993 and January 1995. The randomized group consisted of 40 women and 68 men with a mean age of 34 (range 18–59) years, who were randomized between laparoscopy or conventional appendicectomy. Twenty-four of these patients were excluded from final analysis (*Fig. 1*). The study group comprised 27 women and 57 men with mean age of 34 (range 18–59) years. These patients proved to have acute appendicitis and were treated in accordance with the study protocol (*Fig. 1*). Laparoscopic and conventional appendicectomy were performed in 42 patients each. The two treatment groups were well matched with regard to age, sex, stage of appendicitis, duration of symptoms and preoperative hospital stay (*Table 1*).

Design

The study was carried out as an open, randomized, single-centre study with a single-triangular, sequential design[20]. The patients were equally allocated to either laparoscopic or conventional appendicectomy by block-randomization[21] with a random block size between four and 12. Interim analysis of duration of postoperative convalescence was carried out after every completed randomized block and presented in a single-triangular sequential plot (*Fig. 2*). If the stopping boundaries were crossed by the sample path, the inclusion of new patients would be stopped and the study regarded as conclusive.

Trial procedure

All patients with suspected appendicitis were recorded in the study interval. Patients between 18 and 60 years of age were candidates for randomization. Randomization of patients under 18, although desirable, was considered problematic for medico-legal reasons. Pregnancy, severe cardiopulmonary disease, previous history of peritonitis or major abdominal surgery were exclusion criteria. Written informed consent was obtained. The participating surgeons were experienced in both laparoscopic and conventional appendicectomy. If acute appendicitis was verified, the patients were classified as correctly included in the study group.

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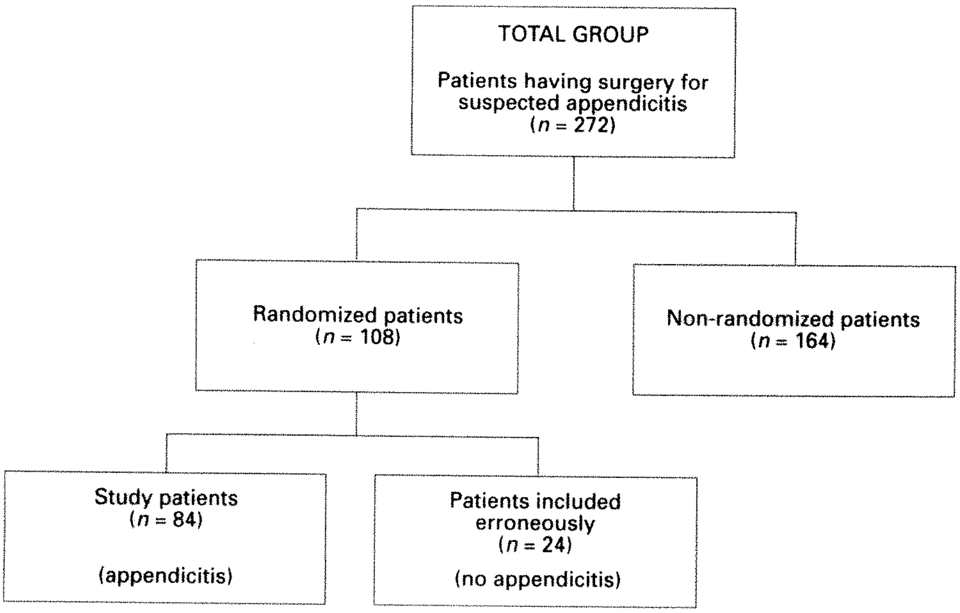

Fig. 1 Flow chart of the entire study

Table 1 Clinical details of study group

	Laparoscopic appendicectomy	Conventional appendicectomy
No. of patients	42	42
Men	31	26
Women	11	16
Stage of appendicitis		
Phlegmonous	22	29
Gangrenous	14	9
Perforated	6	4
Age (years)*	33·9 (18–56)	32·9 (18–59)
Duration of symptoms (h)*	35·6 (8–113)	33·9 (7–158)
Preoperative hospital stay (h)*	10·1 (2–40)	9·1 (2–31)

*Values are mean (range)

Clinical and surgical procedures

Metronidazole 1 g given rectally before surgery was the standard antibiotic prophylaxis for appendicectomy. Patients with known risk factors for venous thromboembolism were given prophylaxis with enoxaparin. Factors and variables recorded included duration of symptoms, preoperative hospital stay, duration of operation, postoperative hospital stay, consumption of analgesic drugs, postoperative pain assessment, complications and postoperative convalescence. Postoperative follow-up until return to normal was determined using a form regarding complications and date of full restitution or return to work. The form was completed by the patients, the general practitioner or by personal contact with the main investigator. Postoperative pain was self-assessed daily using a 10-cm visual analogue scale (VAS) for the first 14 days after operation[22,23].

Diagnostic laparoscopy was performed through an umbilical 10-mm trocar. One or two additional 5-mm trocars were used, if necessary.

For laparoscopic appendicectomy one additional 5-mm and one 10-mm trocar were placed in the right iliac fossa and suprapubically. Bipolar diathermy was used to coagulate the appendix mesentery. The base of the appendix was ligated with two preknotted Roeder loops and divided with scissors. When the specimen was too large for the 10-mm suprapubic trocar, this was replaced by a 20-mm port or a plastic bag was used. Contact between the inflamed appendix and the wound was avoided.

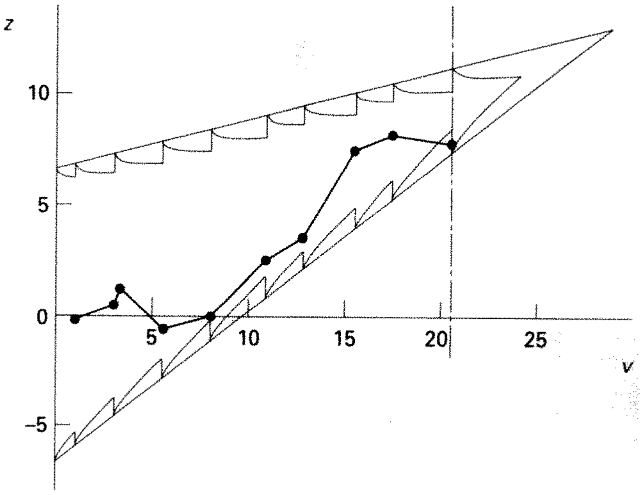

Fig. 2 Sequential design and development of 'duration of postoperative convalescence'. The full lines forming a triangle with the Christmas tree corrections indicate the stopping boundaries. The vertical dotted line indicates the fixed sample design of equivalent power. The sample path is denoted by •——•. A positive z value indicates superiority of laparoscopic appendicectomy. The v value is proportional to the sample size

Conventional appendicectomy was done through a muscle-splitting incision in the right iliac fossa. The arteries in the mesentery and the base of the appendix were simply ligated.

The removed specimen was examined macroscopically and classified as normal or with phlegmonous, gangrenous or perforated appendicitis. The resected specimens were submitted to histopathological examination.

Statistical analysis

All continuously distributed factors and variables were expressed as mean values with total range or 95 per cent confidence intervals. The confidence intervals were constructed by using the Student procedure[24]. Frequencies are expressed in numbers.

The endpoint variable, duration of postoperative convalescence, was used in the sequential, triangular comparison between the two groups[20]. Based on a previous study[10], comparison between the two groups regarding the main variable was carried out one-tailed with a significance level of 5 per cent. The sample size was calculated as if the study had been carried out as a conventional fixed sample trial with a significance level of 5 per cent, power of 95 per cent and a clinically relevant difference in the main variable of at least 15 per cent. The required number of patients to be included was found to be 42 in each group. Investigation of the endpoint variable was carried out for every completed randomized block. The sequential analysis (*Fig. 2*) was based on the general formula of Whitehead[20]. The statistics Z and V are calculated at each inspection. A positive z value would indicate superiority of laparoscopic appendicectomy and a negative value, superiority of conventional appendicectomy. The statistic V is proportional to the sample size. Comparison of the groups with regard to postoperative convalescence, postoperative hospital stay and duration of surgery was carried out by using analysis of variance with sex as covariant[25]. Comparison of pain assessment was performed by using analysis of variance with repeated measurements and sex as covariant[25]. Categorized factors and variables were compared by contingency table analysis[24].

Results

A total of 272 patients had emergency operation for suspected appendicitis. Of these patients 108 were randomized to either initial laparoscopy ($n = 56$) or conventional appendicectomy ($n = 52$). Acute appendicitis was verified in 84 of the randomized patients. In the remaining 164 patients not selected for randomization, 130 had acute appendicitis. The main reason for not randomizing was the age limitation. Additionally, 38 patients could not be randomized because a study investigator was not available, in 31 there was diagnostic uncertainty and three patients refused to participate (*Table 2*). The eligible study population with proven acute appendicitis, who could have been treated in accordance with the trial protocol, consisted of the 84 patients successfully randomized (*Fig. 1*) and 46 who were missed (*Table 2*). The study group represented 30·9 per cent of the total series and 64·6 per cent of the eligible study population. Comparison with the remaining patients in the eligible study population showed significantly ($P < 0{\cdot}01$) more men in the study group. The duration of symptoms and preoperative hospital stay were significantly longer ($P < 0{\cdot}01$) in the remaining eligible study population compared with the study group. However, the study group was found to be representative of the eligible study population regarding age and stage of appendicitis (*Table 3*).

Table 2 Reasons for exclusion from the study related to final diagnosis

	Acute appendicitis	Other diagnosis	Total
Age < 18 years	60	3	63
Age > 60 years	21	4	25
Contraindications	3	1	4
Patient refused	2*	1	3
Uncertain diagnosis	11*	20	31
Investigator not available	33*	5	38
Total	130	34	164

*Patients who were eligible for the study

Twenty-four patients were included erroneously in the randomized group (*Fig. 1*). Of these patients, 14 were randomized to laparoscopy. Diagnostic laparoscopy alone was performed in nine, laparoscopic appendicectomy in two, laparoscopic salpingo-oöphorectomy for adnexal torsion in one, and midline laparotomy for perforated sigmoid diverticulitis in one and suspected malignancy in another. The two laparoscopically removed appendices were found to be normal by histopathological examination. Ten patients were randomized to conventional appendicectomy. In seven of these patients no abnormality needing surgical intervention was detected. Conversion to midline laparotomy was done for bilateral pyosalpinx in one patient and perforated sigmoid diverticulitis in another. In the remaining patient an infected caecal diverticulum required resection through an extended incision in the right iliac fossa. The laparoscopic procedure was found to have a significantly lower risk of unnecessary appendicectomy ($P = 0{\cdot}03$).

Postoperative convalescence was the main variable used in the sequential model. No significant difference was detected in the interim analyses during the study (*Fig. 2*). After inclusion of 42 patients in each group, the difference in favour of laparoscopic appendicectomy was a mean of 4·7 days and close to significance ($P = 0{\cdot}07$) (*Table 4*). However, by comparing the two groups with regard to postoperative convalescence without correction for the analytical inspections, the difference was found to be significant ($P = 0{\cdot}02$). For patients with phlegmonous appendicitis the mean duration of postoperative convalescence was 13·3 days in the laparoscopy group compared with 16·7 days following conventional appendicectomy. The corresponding results for patients with gangrenous or perforated appendicitis were 17·5 and 26·7 days respectively.

Table 3 Representativity of the study group

	Study group ($n = 84$)	Remaining eligible patients ($n = 46$)	Total eligible study population ($n = 130$)
Men	57	20	77
Women	27	26	53
Stage of appendicitis			
Phlegmonous	51	25	76
Gangrenous	23	7	30
Perforated	10	14	24
Age (years)*	33·9 (30·6–37·2)	35·6 (31·6–39·4)	34·5 (32·3–36·7)
Duration of symptoms (h)*	32·9 (27·4–38·4)	63·5 (37·7–89·3)	43·7 (33·7–53·7)
Preoperative hospital stay (h)*	9·6 (8·1–11·1)	16·8 (7·2–26·4)	12·2 (8·7–15·7)

*Values are mean (95 per cent confidence interval)

The duration of surgery was significantly longer for the laparoscopic procedure ($P < 0{\cdot}01$). Regarding postoperative hospital stay, no significant difference was detected ($P = 0{\cdot}27$) (*Table 4*).

The mean number of injections of narcotic analgesics was 3·2 (range 0–14) in the laparoscopically treated group and 4·3 (range 0–58) following conventional appendicectomy. The mean numbers of orally or rectally administered doses of analgesics were 2·6 (range 0–13) and 2·5 (range 0–15) in the two groups respectively. The differences were not statistically significant. The mean levels of pain measured on a 10-cm VAS were 5·0 and 5·4 respectively on the first postoperative day, and reduced to 0·9 in both groups after 14 days ($P = 0{\cdot}62$) (*Fig. 3*).

Minor intraoperative complications occurred in four patients who had laparoscopic appendicectomy compared to three in the other group. Conversion from attempted laparoscopic appendicectomy to laparotomy was not necessary in any patient.

Postoperative complications occurred in 18 patients in the laparoscopic appendicectomy group. Two were classified as serious. Both patients had a pelvic abscess but were successfully treated with antibiotics in combination with percutaneous drainage in one and transvaginal aspiration in the other. Of the remaining patients with minor complications, eight were treated medically only, a superficial wound abscess was opened in one, and seven did not need any treatment.

Postoperative complications occurred in 12 patients in the conventional appendicectomy group. Three were classified as serious: one patient underwent relaparotomy for mechanical small bowel obstruction due to pelvic abscess, another was treated with percutaneous drainage and antibiotics for pelvic abscess, and the third was given antibiotics for inflammation in the ileocaecal region. Of the remaining patients with minor complications, four were managed by medical treatment only, a wound haematoma was drained in one, and four required no treatment.

Seven of 22 patients with phlegmonous appendicitis in the laparoscopic appendicectomy group had complications compared with seven of 29 in the conventional appendicectomy group. The corresponding figures for gangrenous or perforated appendicitis were 11 of 20 patients and five of 13 patients respectively. However, none of these differences in complication rates was statistically significant.

Table 4 Comparison of conventional and laparoscopic appendicectomy

	Laparoscopic appendicectomy ($n = 42$)	Conventional appendicectomy ($n = 42$)
Duration of surgery (min)	51 (45–56)	25 (21–29)
Postoperative hospital stay (days)	3·5 (2·7–4·3)	3·2 (2·3–4·0)
Postoperative convalescence (days)	15·0 (11·6–18·4)	19·7 (15·5–23·9)

Values are mean (95 per cent confidence interval)

Discussion

One limitation of RCTs is that often only a subpopulation of the patients being studied is included[1–6,17–19] because of selection criteria, and for administrative and practical reasons. The selection criteria were kept to a minimum in the present study. The age limitations were most important and caused 62 per cent of the exclusions. This resulted in exclusion of a large and problematic group of female adolescents with suspected appendicitis. Administrative reasons such as unavailability of an investigator and practical reasons including uncertainty of diagnosis, contraindications and patient refusal were

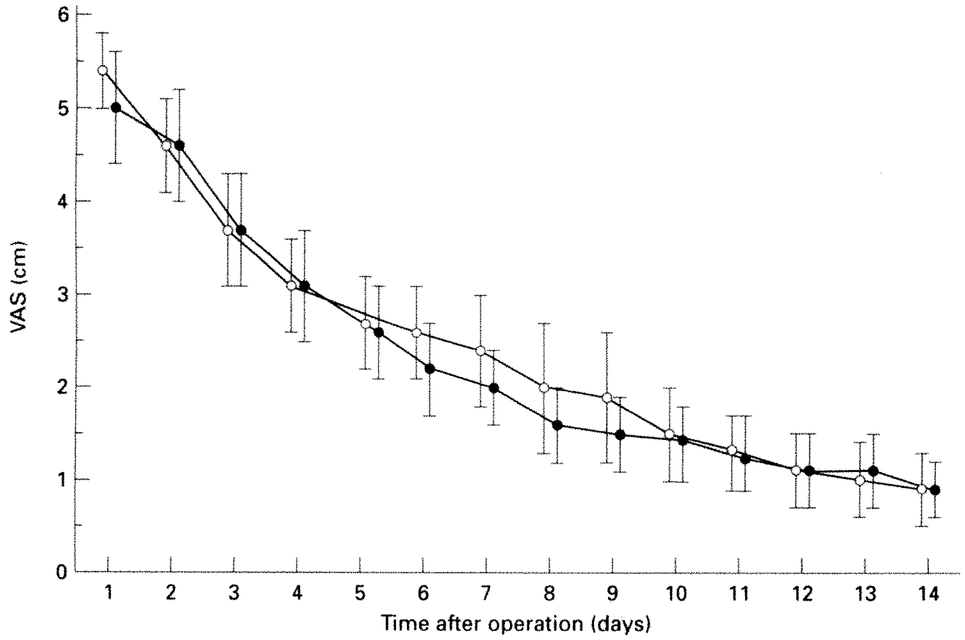

Fig. 3 Postoperative pain in patients who had laparoscopic (●) or conventional (○) appendicectomy. Values are mean with 95 per cent confidence interval. VAS, visual analogue scale

responsible for the remaining missed patients. In spite of the awareness of these difficulties in the planning of the study, 35 per cent of the eligible patients were not included. Compared with other studies[18,19] the rate is low. Populations included in RCTs frequently are not representative with regard to the most important factors in the actual patient populations[17]. To verify the representative nature of the study population, details from everyone in the actual patient population must be recorded. In practice this may be difficult which explains why this problem in relation to RCTs is neither reported nor discussed sufficiently. In the present series the study group was found to be representative of the eligible study population regarding age distribution and stage of appendicitis, but not with regard to sex distribution, duration of symptoms and preoperative hospital stay. Arguably these differences did not influence the validity of the comparison of the two surgical methods. However, if the study group had been found to differ with regard to an important factor such as stage of appendicitis, the validity of the comparison would have been impaired. Such lack of uniformity may be one explanation for conflicting evidence from similar RCTs.

In two randomized studies[15,16] of women with suspected appendicitis it was found that laparoscopy significantly reduced the rate of unnecessary appendicectomy. This was confirmed in the present study which included a majority of men. With inclusion of adolescent women the evidence in favour of laparoscopy might be stronger. Laparoscopy can therefore be recommended in patients with suspected acute appendicitis.

Comparison between the two methods in non-randomized studies[7–14] indicates a large difference in favour of initial laparoscopy. In view of previous experience[10,26] and ethical considerations a sequential design seemed suitable for the present study. However, the estimated difference between the two methods with regard to duration of postoperative convalescence was found to be close to the predefined limits of clinically relevant difference. Consequently, because of corrections in the sequential model[20], the trial was continued until inclusion of 84 patients without reaching significance. By comparing the two groups as if the study had been carried out with an ordinary fixed sample design, the difference in duration of postoperative convalescence was found to be significant in favour of laparoscopic appendicectomy.

The higher frequency of minor complications in the laparoscopically treated group is of little clinical importance. If, however, these complications could effectively be prevented, the advantages of laparoscopic appendicectomy could be enhanced. Although no significant differences between the treatment groups were detected, the complication rates were higher than in other randomized series[1–6].

In subgroup analysis the advantage of laparoscopy in reducing postoperative convalescence was greatest for gangrenous or perforated appendicitis, in contrast to the conclusions of others[7,11], who recommend conventional operation in these cases. In other randomized series perforated appendicitis was among the reasons for conversion to laparotomy[1–3,5,6], and in one study patients with perforation were not included[4].

Because the study was not carried out blindly, possible investigator bias cannot be eliminated. The significantly longer duration of the laparoscopic procedure and the failure to reduce postoperative hospital stay lessens the assumed advantages of laparoscopic appendicectomy in relation to the conventional procedure. The present study did not reveal any significant difference between the two methods regarding analgesic requirement, postoperative pain assessment or complications.

Comparing randomized[1–6] and non-randomized[7–14] studies of conventional *versus* laparoscopic appendicectomy, the advantage of the laparoscopic procedure seems to be less marked in the randomized trials. In a previous non-randomized study[10] the mean difference in duration of postoperative convalescence was 6·3 days compared with 4·7 days in the present randomized study. This difference might be attributed to selection of patients as well as experience of the participating surgeons. In the non-randomized studies conventional appendicectomy is usually performed by trainee surgeons, and the laparoscopic operation by experienced surgeons. In the randomized series, however, both operations are performed by surgeons with extensive experience. This might reduce differences between the two methods. Additionally, the patients selected for laparoscopic appendicectomy in non-randomized studies might be more suitable for the laparoscopic procedure than patients allocated in randomized trials.

In conclusion, because of selection procedures, and for administrative and practical reasons, it was difficult to obtain a well matched study group with regard to all important factors for acute appendicitis, although by focusing on this problem during the trial, it was possible to achieve a reasonable match regarding the most important factors. The laparoscopic approach for patients with suspected appendicitis improves the diagnostic accuracy, and is therefore recommended. In patients with verified acute appendicitis laparoscopic appendicectomy is at least as good as conventional appendicectomy. The advantage of shorter convalescence is balanced against a longer operation.

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Randomized placebo-controlled trial of teicoplanin in the antibiotic prophylaxis of infection following manipulation of burn wounds

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Background Burn wound surgery or change of dressings commonly causes bacteraemia. The use of antibiotic prophylaxis has not been tested adequately in a controlled trial.

Methods A randomized double-blind placebo-controlled study was performed to determine the effect on Gram-positive bacteraemia and clinical outcome of a single dose of teicoplanin (12 mg/kg intravenously) given at burns surgery or change of dressings.

Results A total of 134 patients were entered into the study, representing 220 episodes of dressing or debridement (110 episodes in each group). There was a significant difference between the groups with respect to perioperative Gram-positive bacteraemia: eight episodes (7 per cent) in the teicoplanin group *versus* 51 (46 per cent) in the placebo group ($P < 0.001$). However, good clinical outcome was similar in both groups (80 of 110 *versus* 77 of 110 respectively, $P = 0.7$). Only eleven patients had bacteraemia caused by Gram-negative species alone. Bacteriological response in terms of wound culture showed no significant difference between the groups: 63 (57 per cent) of 110 episodes *versus* 58 (53 per cent) of 110 respectively respectively.

Conclusion Prevention of Gram-positive bacteraemia did not affect postoperative recovery.

Wound infection remains a major cause of morbidity and mortality in burned patients despite the increasing use of early tangential excision[1]. *Staphylococcus aureus* is the most common isolate from burn wounds and in many units methicillin-resistant strains (MRSA) colonize the burn. Although pathogenicity is similar to that of methicillin-sensitive strains, MRSA is an easily identified marker of cross-infection, and discharge of patients to other wards or hospitals becomes difficult. *S. aureus* is responsible for the potentially fatal toxic shock syndrome in children with scalds[2]. *Streptococcus pyogenes* is an occasional but devastating cause of graft loss, and surgery usually has to be postponed if it is detected. The Gram-negative bacteria, particularly *Pseudomonas aeruginosa* and *Acinetobacter* species, colonize and infect burn wounds during the second week after injury and cause late bacteraemia.

Attempts to prevent burn wound infection have been directed towards delaying colonization by topical agents, source isolation and the use of ventilated rooms for dressing changes. Most burns units use topical silver sulphadiazine to slow pseudomonal colonization of the burn[3]. Topical agents have been shown to reduce significantly graft failure in moderately sized burns and the mortality rate has fallen since their introduction[4]. Routine administration of systemic antibiotics from the time of admission does not prevent wound colonization and selects for a more resistant bacterial flora. Attempts at the prevention of streptococcal cellulitis generally have been abandoned after controlled trials showed no significant benefit[5]. Burn wound surgery or change of dressings induces bacteraemia in up to 46 per cent of patients in the absence of antibiotics but in only 1·6 per cent of those given antibiotics[6–8]. Many units use perioperative antibiotics to prevent bacteraemia and wound infection[3], but there is little trial evidence to support the practice. Prophylaxis is beneficial in surgery to old healed burns[9] and has been shown to reduce bacteraemia significantly in burns affecting over 60 per cent of total body surface area (TBSA)[10].

Teicoplanin (Roussel, Denham, UK) should be a suitable choice for prophylaxis in these patients because of its activity against MRSA and streptococci. It has a long serum half-life and, unlike vancomycin, it can be given as a bolus dose just before operation[11]. A double-blind placebo-controlled trial was undertaken to determine whether the use of teicoplanin before manipulation of the burn wound would prevent Gram-positive bacteraemia and improve clinical outcome, reducing the incidence of burn wound infection and graft loss after the procedure.

Patients and methods

Design

This randomized double-blind study compared a single dose of teicoplanin with placebo for the prevention of infection in burns surgery or at change of dressing. A single dose of teicoplanin (12 mg/kg intravenously) or placebo was administered at the time of induction of general anaesthesia or immediately before the start of the dressing change. Teicoplanin was dissolved in 50–100 ml normal saline to obscure the slight colour imparted by it.

All microbiological specimens were processed at a single laboratory. The patients and all staff, except the pharmacist, were unaware of the study treatment administered. Consecutive patients fulfilling the inclusion criteria were randomly assigned treatment according to a schedule produced by Hoechst Marion Roussel. Patients were stratified according to age above or below

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12 years. The study was conducted in accordance with the Declaration of Helsinki (Tokyo Revision) and under a CTX (UK regulatory authority approval). The protocol was approved by the ethics committees of participating hospitals. Informed consent was obtained from all subjects before participation.

It was intended to recruit sufficient patients for 300 episodes of treatment. The estimation of sample size was based on the ability to distinguish a proportion of wounds colonized with *S. aureus* of 50 per cent *versus* 30 per cent after surgery, or a burn wound infection rate (more than 10^5 organisms per g) of 18 *versus* 5 per cent, each with a power of 0·9.

Wound management

Early tangential excision of full-thickness burns was performed at a median of 5 days. Superficial burns were dressed with tulle gras, and deeper burns with silver sulphadiazine with or without cerium nitrate. Silver sulphadiazine or 0·5 per cent chlorhexidine was applied at dressing changes to delay bacterial colonization. Cerium nitrate-containing preparations were used to provide a firm eschar to avoid heavy colonization and promote healing when early surgery was not performed.

Recruitment

All adults and children having burns surgery or change of dressings to unhealed burns were considered. Inclusion criteria were: (a) patient age of 2 months or more; and (b) burns requiring hospital admission, except inhalation injury alone. Exclusion criteria were: (a) debridement within 6 h of injury; (b) antibiotics administered within 48 h before the procedure, except benzylpenicillin used to prevent inhalation injury pneumonia; (c) hypersensitivity to glycopeptides; (d) pregnancy or lactation; (e) proven respiratory or urinary tract infection; and (f) surgery or trial entry within the previous 72 h.

Bacteriology

Blood cultures were collected at four points: immediately before, during and at the end of the procedure, and on return to the ward. The minimum inhibitory concentration (MIC) of blood culture isolates was determined in Iso-sensitest broth (Oxoid, Basingstoke, UK). Minimum bactericidal concentrations (MBCs) were determined for staphylococci (99·9 per cent bacterial killing).

Wound infection was assessed by means of a burn wound biopsy and semiquantitative surface swabs, as described previously[12,13]. Biopsies were taken, where possible, under anaesthesia in burn wounds that were not already excised or grafted or entirely superficial. Semiquantitative surface swabs were collected in parallel in these patients but were the only sample in those from whom biopsies could not be obtained. The MIC of teicoplanin for wound isolates was determined by an agar dilution method.

Outcome

Three primary outcome definitions were used at 3 days: clinical response, bacteriological response – blood, and bacteriological response – wound (*Table 1*). A secondary infection was defined by a new fever and new infection at other sites: urinary infection – significant bacteriuria in two successive midstream urine specimens or catheter specimen plus similar blood isolate; respiratory infection – three of the following: fever (temperature greater than 38°C), white blood count more than 15×10^9/l, increase and purulence of tracheobronchial secretions or worsening pulmonary gas exchange; intravenous line infection – erythema and tenderness at the line site, purulent discharge or positive blood culture with a similar organism from a peripheral site and drawn through the catheter.

Statistical analysis

The database was analysed using the Statistical Analysis System, version 6.04 (SAS Institute, Cary, North Carolina, USA). Continuous data were checked for normality with Wilk's test, and summarized accordingly. The two treatment groups were compared with Student's two-sample t test, the Wilcoxon rank sum test, a χ^2 test or Fisher's exact test as appropriate[14]. The proportion of failures on each assessment was compared, allowing for the two age groups, using a Cochran–Mantel–Haenszel χ^2 test. Unevaluable results were excluded; success and success with complications were combined (*Table 1*). Patients entering the study for the first time, those having dressings or debridement, and those with burns affecting more than 15 per cent or 30 per cent of TBSA were also analysed separately.

Table 1 Definitions of outcome at 3 days

Outcome	Success	Failure	Unevaluable
Clinical	No antimicrobials used other than the study drug; no appearance of fever (temperature greater than 38°C if not present before surgery); no new rigors or hypotension or loss of graft	Other antimicrobials used; surgical procedures needed due to infection; new fever with rigors or hypotension; death thought to be due to sepsis; loss of more than 5 per cent of graft	Protocol violation or death within 3 days not thought to be due to sepsis
Bacteriological blood	Negative blood cultures during and after surgery. With complications: Gram-negative isolates only	Gram-positive organisms in blood culture	Failure to collect three blood cultures
Bacteriological wound	Fewer than 10^5 organisms per g wound biopsy or fewer than 10^4 organisms per cm^2 from surface alginate swabs; more than 100-fold reduction in Gram-positive bacterial count of biopsy or swab between surgery and 48 h. With complications: as above with the appearance of more than 10^5 Gram-negative organisms per g biopsy or 10^4 Gram-negative organisms per cm^2 from surface alginate swabs	More than 10^5 Gram-positive organisms per g wound biopsy or more than 10^4 Gram-positive organisms per cm^2 skin from alginate swabs, or less than 100-fold reduction in counts of Gram-positive bacteria between the time of operation and 48 h	Failure to collect two biopsies or alginates unless the wound was fully grated with no graft failure; more than 10^5 Gram-negative organisms only on operative and 48-h biopsy or swab

Laboratory data were summarized with quartiles, and differences tested with a Wilcoxon rank sum test[14]. As patients could be entered more than once, an episode was used to mean a period of study evaluation following treatment with teicoplanin or placebo.

Results

Study population

The total number of episodes was 220: 110 episodes of teicoplanin prophylaxis and 110 of placebo prophylaxis in 134 patients (*Tables 2* and *3*). Some patients received both teicoplanin and placebo on at least one occasion. Of the 134 patients who were treated for at least one episode during the study, 67 received teicoplanin and 67 placebo for the first episode of prophylaxis. There were no significant differences between the groups with respect to all patients or those entering for the first time. Surgical and topical management of the burns and the use of other medicines were similar in both groups. Two patients were unevaluable for efficacy but both were included in the safety assessment. Three patients died, but all were assessable for efficacy.

Table 2 Demographic information for all episodes

	Teicoplanin ($n = 110$)	Placebo ($n = 110$)
Sex ratio (M:F)	80:30	82:28
Age (years)	38·0 (23–54)	42·5 (26–56)
Height (cm)		
Women	162 (150–168)	157 (150–165)
Men	175 (168–178)	175 (168–179)
Weight (kg)		
Women	59·0 (46–70)	55·8 (30–70)
Men	72·0 (62–80)	74·6 (67–82)
Systolic blood pressure (mmHg)	120 (110–130)	118 (110–135)
Diastolic blood pressure (mmHg)	70 (59–80)	70 (60–80)
Heart rate (per min)	88 (80–105)	89 (80–100)
Temperature (°C)	37·0 (36·6–37·4)	37·0 (36·5–37·4)

Values are median (interquartile range)

Table 3 Burn and operative details for all episodes

Burn characteristic	Teicoplanin ($n = 110$)	Placebo ($n = 110$)
TBSA (%)*	8·5 (4–18)	8·0 (4–16)
Time from day of burn*	8 (3–19)	9 (3–23)
Full thickness	49 (45)	50 (45)
Partial thickness	61 (55)	60 (55)
Scald	33 (30)	31 (28)
Chemical	4 (4)	2 (2)
Thermal	73 (66)	77 (70)
Duration of operation (h)*	1·1 (0·8–1·5)	1·1 (0·8–1·6)
Recovery time (h)*	0·8 (0·5–1·0) ($n = 45$)	0·7 (0·5–1·0) ($n = 51$)
Volume of blood loss (litres)*	0·2 (0·08–1·0) ($n = 41$)	0·5 (0·1–0·9) ($n = 45$)
Dressing	63 (57)	61 (55)
Debridement	47 (43)	49 (45)

*Values are median (interquartile range); other values in parentheses are percentages. TBSA, total body surface area

Clinical outcome

There was no significant difference between the clinical response in the two treatment groups, taking into account the two age groups (95 per cent confidence interval for difference in proportions −0·09–0·15, $P = 0{\cdot}7$ (*Table 4*). This result was not affected by excluding patients in whom Gram-negative bacteraemia (alone) was detected during the procedure or those entering for the second or a subsequent time. There were no significant differences in the causes of failure in the two groups. Of the 61 failures (placebo 32 *versus* teicoplanin 29), 32 (20 *versus* 12) involved additional antibiotic treatment, 40 (19 *versus* 21) had fever, four (three *versus* one) had rigors and three (two *versus* one) had hypotension. In the placebo group, 15 of the patients had grafts, seven of which failed (median loss 50 per cent) compared with 18 grafts in the teicoplanin group, of which four failed (median loss 15 per cent) (P not significant).

There was no significant difference between the groups in the number of febrile days in the first week (maximum temperature greater than 37·2°C) after manipulation of the burn wound (Mann–Whitney U test). The incidence and nature of secondary infections was similar in the two groups (*Table 4*). Gram-negative bacteria caused ten of the infections in the placebo group, five of which were treated, and nine of the infections in the teicoplanin group, four of which were treated. Daily assessment of general status showed no significant differences between the groups throughout the week following the procedure.

Bacteraemia

There was a highly significant difference between the treatment groups with respect to the incidence of positive blood cultures ($P < 0{\cdot}001$) (*Table 5*). There were significantly more blood isolates of *S. aureus* ($P < 0{\cdot}001$, Fisher's exact test), coagulase-negative staphylococci ($\chi^2 = 13$, 1 d.f., $P < 0{\cdot}001$) and *Corynebacterium* species in the placebo group ($P = 0{\cdot}004$, Fisher's exact test). There was no significant difference in the number of isolates of

Table 4 Clinical outcome for all and first episodes

Clinical outcome	All episodes		First episodes	
	Teicoplanin	Placebo	Teicoplanin	Placebo
Success	80 (73) [9]	77 (70) [10]	46 (69)	44 (66)
Failure	29 (26) [4]	32 (29) [2]	21 (31)	23 (34)
Unevaluable	1 (1)	1 (1)	0 (0)	0 (0)
Total	110 (100) [13]	110 (100) [12]	67 (100)	67 (100)
Secondary infection	14 (13)*	17 (15)†	10 (15)	13 (19)

Values in parentheses are percentages; values in square brackets are the number of children aged under 12 years. *Respiratory: five episodes (*Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (two), *Candida* species); urinary: ten episodes (*Proteus* species, coliform, *Klebsiella* species, *Escherichia coli* (five), *Enterococcus faecalis*, *Candida* species); soft tissue: four episodes (*S. aureus* (two), coagulase-negative staphylococcus, unknown). †Respiratory: seven episodes (*P. aeruginosa*, *H. influenzae*, *S. aureus* (two), unknown (three)); urinary: nine episodes (*Proteus* species (four), *E. coli* (three), *Enterobacter cloacae*, *E. faecalis*); soft tissue: three episodes (*S. aureus* (two), *P. aeruginosa*). Some patients had more than one site of secondary infection

Gram-negative species. In the placebo group, there were ten episodes of Gram-negative bacteraemia, nine probably originating from the burn, and two further episodes diagnosed clinically but culture negative. Two patients acquired a nosocomial respiratory infection, and one had a pseudomonal urinary infection which was not treated. In the teicoplanin group, there were seven episodes (seven patients) of Gram-negative bacteraemia, five related to the burns and two clinically diagnosed cases. Six patients in the teicoplanin group and five in the placebo group had bacteraemia with Gram-negative species alone. No patient in either group was shown to develop metastatic Gram-negative infection.

Results for first episodes were similar (placebo *versus* teicoplanin: Gram-positive 31 of 67 *versus* six of 67, Gram-negative three of 67 *versus* four of 67), as was analysis of episodes 1–7 or 8–15 days after injury.

Wound cultures

There was no significant difference between the bacteriological response on wound culture in the two treatment groups, taking into account the two age groups ($P = 0{\cdot}1$) (*Table 5*). The bacterial species present in the wound were similar before and after antibiotic administration (*Table 6*). No significant difference between the groups was demonstrated by applying a threshold to the bacterial numbers or by analysis of burns at 1–7 or 8–15 days after injury, or first or all episodes. If routine surface swabs taken in the first week after the procedure were included, *S. aureus* was isolated from the burns of significantly fewer patients in the teicoplanin group (55 (50 per cent) of 110 *versus* 76 (69 per cent) of 110, $P < 0{\cdot}01$).

Table 5 Bacteriological outcome for all episodes

Bacteriological outcome	Teicoplanin ($n = 110$)	Placebo ($n = 110$)
Blood		
Success	90 (82)	51 (46)
Success with complications	6 (5)	5 (5)
Failure	8 (7)	51 (46)
Unevaluable	6 (5)	3 (3)
Wound		
Success	63 (57)	58 (53)
Success with complications	10 (9)	4 (4)
Failure	28 (25)	39 (35)
Unevaluable	9 (8)	9 (8)

Bacterial susceptibility to teicoplanin

In the teicoplanin group, but not in the placebo group, the MIC of teicoplanin for all Gram-positive isolates was significantly higher in the first week after the procedure than at the time of the procedure (median 1·0 *versus* 0·5 mg/l, $P = 0{\cdot}002$, Mann–Whitney *U* test). Resistance to teicoplanin (defined as MIC greater than 16 mg/l) was present only in coagulase-negative staphylococci. At the time of the procedure, three of 45 isolates in the teicoplanin group were resistant, compared with one of 67 in the placebo group. The MIC$_{50}$ (MIC inhibiting 50 per cent of strains) for *S. aureus* in all analyses was 0·5 mg/l for methicillin-sensitive strains and 1·0 mg/l for MRSA. Similarly, for *Enterococcus faecalis* the MIC$_{50}$ was 0·25–0·5 mg/l. In one of 16 coagulase-negative staphylococci in the teicoplanin group and in four of 38 in the placebo group, the MBC was 32 mg/l (all *S. haemolyticus*). In addition, two of 26 blood isolates of *S. aureus* in the placebo group had an MBC of 32 mg/l.

Subgroup analysis

Similar results were obtained in the teicoplanin and placebo groups by considering only burns of over 15 per cent TBSA or only dressing changes, either first or all episodes. With burns of over 30 per cent TBSA, nine of 12 episodes were clinically successful in the teicoplanin group and four of nine in the placebo group (*P* not significant). If debridements only were considered (of any

Table 6 Isolates from blood and wound cultures

	Placebo ($n = 110$)			Teicoplanin ($n = 110$)		
Species	Blood (no. of isolates)	Biopsy (no. with $> 10^5$ c.f.u. per g)	Alginate (no. with $> 10^4$ c.f.u. per cm^2)	Blood (no. of isolates)	Biopsy (no. with $> 10^5$ c.f.u. per g)	Alginate (no. with $> 10^4$ c.f.u. per cm^2)
Corynebacterium species	9	2	3	0	3	3
Enterococcus faecalis	1	6	1	0	2	2
MSSA	21	9	26	1	11	27
MRSA	3	4	12	0	2	6
Coagulase-negative staphylococci	39	2	6	11	4	8
Streptococcus group A	0	0	0	0	1	1
Other Gram-positive species	15	1	9	0	1	0
Acinetobacter species	1	2	4	1	3	7
Enterobacter species	5	2	10	0	1	7
Klebsiella species	3	2	6	0	0	2
Pseudomonas aeruginosa	7	6	14	8	2	8
Other Gram-negative species	3	5	6	2	2	6
Candida species	0	0	1	0	0	0
No growth	243	8	13	305	7	20
Total no. of specimens	327	38	109	323	37	106

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*; c.f.u., colony-forming units extent), there were significantly more bacteriological failures based on wound culture in the placebo group (nine of 47 *versus* 19 of 49, $P = 0{\cdot}02$).

Adverse events

At least one adverse event was reported for 24 (22 per cent) of the episodes for which the subjects received teicoplanin and for 15 (14 per cent) following placebo ($P = 0{\cdot}1$). In the teicoplanin group, nine adverse events in seven patients were thought possibly to be related to the study drug, compared with four in four patients in the placebo group. The assessment was made before the randomization code was broken.

The most common adverse event was abnormal liver function, usually a raised alkaline phosphatase or aspartate transaminase concentration, occurring in eight (7 per cent) of the teicoplanin group and five (5 per cent) of the placebo group. There was spontaneous resolution in all cases. Three and two episodes respectively were thought to be related to study medication. Three patients in the teicoplanin group developed a pruritic rash possibly related to the antibiotic and were not re-entered into the trial. Four others complained of pruritus. There were no patients with rash or pruritus in the placebo groups. No severe adverse events were thought to be related to study medication. Three patients died as the result of burn injury (one in the teicoplanin group, two in the placebo group). There were no significant differences between the treatment groups for any haematological or biochemical variable (Wilcoxon rank sum test for differences).

Discussion

Teicoplanin administered as a single dose at the start of burns surgery or dressing change was effective in preventing bacteraemia due to Gram-positive organisms but the postoperative clinical course was not significantly different in patients given teicoplanin from that in those given placebo. For wounds that were debrided, there were more bacteriological failures in the placebo group.

Pharmacokinetic behaviour of antibiotics in burned patients is highly variable and clearance of vancomycin is increased compared with that in normal subjects[15]. However, tissue concentrations of teicoplanin were adequate to inhibit or kill most pathogens[16]. Six hours after a dose of 12 mg/kg, the median serum level was 18·4 (range 11·4–28·1) mg/l) in adults and 15·5 (range 11·6–19·1) mg/l in children.

Although the MIC of teicoplanin for Gram-positive isolates rose in patients given teicoplanin, only three isolates had an MIC greater than 16 mg/l at the time of the procedure. Two of 26 blood isolates of *S. aureus* and five of 54 blood isolates of coagulase-negative staphylococci had an MBC of 32 mg/l. Bacteria inhibited but not killed *in vivo* may not have been cultured from the blood because of the presence of a low concentration of teicoplanin in the blood culture medium. Teicoplanin kills growing, not resting, cells[17,18] and against some strains of *S. aureus* the antibiotic is bacteriostatic in the presence of serum[19,20]. The MBC_{90} (MBC killing 90 per cent of strains) of both glycopeptides for *S. aureus* is 16–32 mg/l despite an MIC_{90} of 4 mg/l or less[21,22], and the difference between MIC and MBC has been blamed for a recent failure of treatment of septicaemia[23]. The rate of bacterial killing by teicoplanin, like that of vancomycin, is often slow and is independent of concentration[24,25].

There was no significant difference in the duration of fever after the procedure following placebo or teicoplanin.

The failure to show an effect on outcome might have been the result of inadequate numbers of patients, but the observed success rates were well balanced between the groups. Re-entry of some patients did not appreciably bias the results because outcome was not affected when only first episodes were analysed. Gram-negative bacteraemia was not common and did not cause Gram-negative infection at other sites. Inclusion of many smaller burns could have obscured the outcome, but analysis of patients with burns greater than 15 per cent of TBSA again produced similar results. Examination of wound debridement alone showed no difference in the clinical course except with respect to wound bacteriological outcome.

The use of antibiotic prophylaxis in burn wound surgery or manipulation is common practice in some UK burns units and in the USA, where many units use a first-generation cephalosporin[3], but its routine use has been questioned[26]. Perioperative cephalothin was effective in reducing infection in a double-blind placebo-controlled trial[9] of patients having reconstructive grafts to old healed burns (seven of 122 *versus* one of 127, $P = 0{\cdot}06$). During excision of acute burns of over 60 per cent TBSA, bacteraemia, but not sepsis, has been reported to be significantly more common in patients given placebo compared with a cephalosporin[10]. In the absence of antibiotics, between 21 and 46 per cent of procedures are associated with bacteraemia but only 3 per cent (two of 58) develop clinical sepsis[6,7]. When systemic antibiotic prophylaxis was used, Petersen *et al.*[8] found only one positive blood culture in 46 patients having burn excision. Serial sampling detects much higher rates. One study compared 28 patients given aminoglycosides during repeated excisions, dressings or other procedures[27]. Bacteraemia (mostly staphylococcal) was demonstrated during 45 per cent (50 of 112) of excisions but only nine patients had positive cultures 1 h later. Three of these had a rise in fever or pneumonia but none developed sepsis.

The use of teicoplanin as prophylaxis in this study was safe, most adverse events being mild or compatible with severe burns. Overall, nine events in seven patients were thought related to the study drug compared with four events in four patients in the placebo group. Abnormalities of liver function were most common in both treatment groups. Teicoplanin has been associated with reversible hepatic dysfunction in 57 (2 per cent) of 3377 patients treated in clinical trials[28]. Rash has been the most common adverse effect in most other trials (3 per cent of 3377)[28].

Serum and tissue concentrations following a single dose of teicoplanin were sufficient to prevent Gram-positive bacteraemia during manipulation of the burn wound and reduced the number of Gram-positive bacteria on the wound following debridement. However, the use of teicoplanin did not significantly affect clinical outcome or graft failure.

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Short note

The NIM-2 nerve integrity monitor in thyroid and parathyroid surgery

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Experience using a new nerve stimulator system to assess recurrent laryngeal nerve function during thyroid and parathyroid dissection is presented.

Patients and methods

Stimulation of a peripheral motor nerve produces a myoelectric impulse over the relevant muscle. The NIM-2 nerve integrity monitor (XOMED Surgical Products, Crowthorne, UK) uses a specially designed endotracheal tube with electrodes along its sides (*Fig. 1*) to detect these impulses when the recurrent laryngeal nerve is stimulated at operation.

Fifteen recurrent laryngeal nerves in 12 patients were dissected by three surgeons during routine thyroid and parathyroid surgery. Surgeons scored on a pro forma (arbitrary scale from 1 to 10) an assessment of the help provided by the nerve integrity monitor during various parts of the operation. Anaesthetic staff were asked to comment on each patient. Clinical assessment of the vocal cord function was made before operation and at 0 and 6 weeks after surgery.

Results

Thirteen of the 15 nerves were successfully identified by the integrity monitor. Faulty endotracheal tube electrodes were the cause of failure in one patient. In the other patient a parathyroid adenoma was lying in a superficial position and dissection of the nerve was not required. In the 13 completed patients, surgeons scored a median of 10 for help in confirming visualization of the nerve and 10 for help in demonstrating an intact nerve at the end of the procedure. A median score of only 5 was given for help in identifying the nerve before visualization.

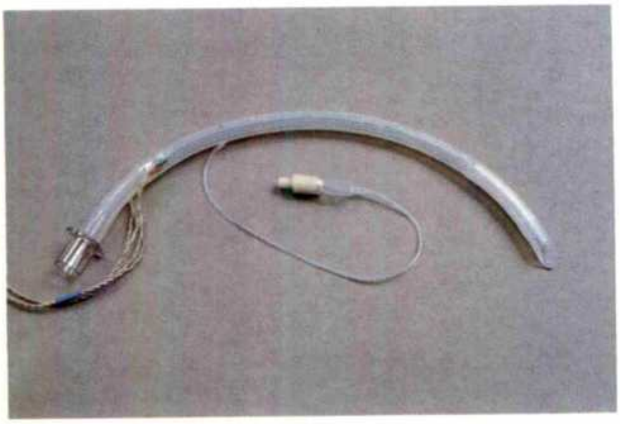

Fig. 1 The specially designed endotracheal tube used to monitor electromyographic signals in the vocal cords at operation

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Anaesthetic problems reported were that the purpose-built endotracheal tube was too soft, permitting kinking and obstruction and positioning marks on the tube were not clearly visible. Some anaesthetists felt it a disadvantage that paralysing agents could not be used during the procedure. No postoperative recurrent laryngeal nerve damage was detected clinically.

Discussion

Identifying the recurrent laryngeal nerve during thyroid surgery is an important step in reducing the incidence of iatrogenic vocal cord palsy[1].

Techniques relying on cord movement as an indication of recurrent laryngeal nerve function[2–4] have proved too cumbersome for routine clinical use. An electromyographic method for monitoring recurrent laryngeal function has recently been demonstrated in animals[5] and the authors' experience with a system designed for clinical use is described here. The NIM-2 system is a significant advance and one which with a little more modification of the endotracheal tube could be suitable for routine use in thyroid and other neck surgery.

Demonstration of an intact recurrent laryngeal nerve at the end of surgery is reassuring and of medicolegal significance. The system was not a substitute for careful dissection in locating the nerve. A possible disadvantage of any system relying on stimulation of a nerve along its length is that it will not detect damage proximal to the point of stimulation.

The basic price of the NIM-2 system is £6500 and disposable costs for each patient were significant at £156.

Acknowledgements

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Surgical treatment for carcinoma of the oesophagus in Chinese language publications

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Introduction This review is a meta-analysis of Chinese language publications on surgical treatment for oesophageal cancer.

Methods Between 1980 and 1994, 17815 patients had surgery for carcinoma of the oesophagus. The male:female ratio was 3·9:1 and mean age was 51·9 (range 16–80) years.

Results Mean resectability rate was 86·7 per cent and hospital mortality rate was 3·8 per cent. The crude 5-year and 10-year survival rates for all patients were 29·6 and 16·4 per cent respectively. For patients with stage 0 and stage I tumours, the 5-year survival rate was 95 and 89 per cent respectively, significantly greater than that for those with stage II, III and IV tumours (19·4 per cent, $P < 0·01$). The 5-year survival rate of all 2226 patients with tumour resection after radiotherapy was 38·0 per cent. There was no significant difference in survival following combination therapy compared with surgery alone. When compared with a report for the interval 1940–1979, there was no significant difference in the resectability, hospital mortality or 5-year survival rates.

Conclusion Oesophageal carcinoma remains a disease with dismal prognosis but surgery still offers the best chance of long-term survival. Adjuvant therapy has not yet proved an advantage in terms of survival but can be useful for palliation. Mass screening might improve survival but only in a population with a high incidence of oesophageal carcinoma.

Carcinoma of the oesophagus is an important cause of mortality and morbidity in certain areas, particularly in North China[1]. The results of surgical treatment of oesophageal carcinoma have been reviewed extensively in the English language literature. However, data from the People's Republic of China, a country with approximately one-fifth of the world's population, have not been readily available in the English-speaking world. In recent years the Chinese have published numerous articles on this topic. This report is a review of Chinese language publications from 1980 to 1994 designed to evaluate the results of these studies.

Patients and methods

Meta-analysis was performed according to the methods of Sacks *et al.*[2] and L'Abbe *et al.*[3]. All Chinese language publications between 1980 and 1994 listing surgery for carcinoma of the oesophagus and survival rates from *Chinese Literature of Science and Technology* (*Medicine*) (published by the Medical Information Institute of China, Beijing) were reviewed. Case reports, reviews and abstracts were excluded. The inclusion criteria were as follows. (1) The paper must be a full article published in a nationally available medical journal. (2) Subjects of the study should be patients undergoing operation for oesophageal cancer. (3) Carcinoma of the oesophagus should be confirmed by histological findings. (4) No fewer than 300 patients should be included in each study. (5) Where more than one paper arose from a single centre, only the latest publication was chosen. (6) The results should be derived from cross-sectional studies with appropriate design and reporting.

Of the 24 papers reviewed, seven were excluded from analysis because of incomplete information or involvement of selected patient groups (e.g. sex, age). The remaining 17 papers were included in the study[4–20]. Because of the different origin of the patients' records, there was some bias in the quality, as well as quantity, of the available information. Data are presented as mean(s.d.) in each of the subgroups.

Results

Patients

During the period under review, a total of 17815 patients were reported who had surgery for carcinoma of the oesophagus. There were 14176 male and 3636 female patients (M:F ratio 3·9:1). Mean(s.d.) age was 51·9(0·6) (range 16–80) years. Diagnosis of oesophageal carcinoma was made by barium studies and oesophagoscopy with confirmatory histological testing in all patients. Some 8·8 per cent of all tumours were located in the proximal third of the oesophagus, 65·9 per cent in the middle third and 25·3 per cent in the distal third. Squamous cell carcinoma accounted for 97·6 per cent of all tumours; 2·4 per cent were adenocarcinomas.

Mortality and morbidity

Mean resectability rate was 86·7(5·2) per cent. In one large report involving 6123 cases, the resectability rate was as high as 93·7 per cent[11].

Mean(s.d.) operative mortality rate at 30 days was 3·8(1·8) (range 0·3–6·4) per cent. Causes of death included anastomotic leakage (3·9 per cent), empyema (3·3 per cent), myocardial infarction (1·0 per cent) and respiratory failure (2·1 per cent).

The most common postoperative complication was intrathoracic anastomotic leak with an incidence of 3·9(0·9) per cent, followed by postoperative wound infection, reported in 3·3(2·1) per cent of patients. Other complications included myocardial infarction, respiratory complications and chylothorax.

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Tumour staging

Staging was done using the postsurgical resection classification (pathological tumour node metastasis (pTNM)) as developed by the American Joint Committee on Cancer[21]: stage 0 ($T_{is} N_0 M_0$), 0·7 per cent; stage I ($T_1 N_0 M_0$), 3·4 per cent; stage II ($T_2 N_0 M_0$), 16·3 per cent; stage III ($T_3 N_0 M_0$ or any T $N_{1-3} M_0$), 51·1 per cent; and stage IV (any T $N_{1-3} M_1$), 26·8 per cent.

Preoperative radiotherapy

Some 2226 of 17815 patients received preoperative radiotherapy (combined therapy group). Most of the patients were selected for combined therapy because of questionable resectability as evaluated on clinical grounds. Classification by the pTNM system showed that the 2226 cases included 70·2 per cent with stage III and 15·8 per cent with stage IV tumours. No patients with stage 0 or stage I tumours had preoperative radiotherapy.

Preoperative radiotherapy was given with a linear accelerator by means of two parallel opposed portals. Re-evaluation was performed 4 weeks after a total dose of 40 Gy. In irradiated patients the resectability and operative mortality rates were 90·5(1·2) and 3·8(0·5) per cent respectively. The 5-year survival rate of all 2226 patients having combination therapy was 38·0(2·8) per cent.

Survival

Crude survival data were reported as the percentage of the total number of patients who underwent resection, from 1 to 5 years. Survival values were calculated by life-table analysis, and postoperative mortality was included. The crude 5- and 10-year survival rates for oesophageal cancer were 29·6(8·3) and 16·4(5·6) per cent respectively. Five-year survival rates varied from 12·6 to 47·1 per cent. For patients treated for stage 0 and stage I tumours, the estimated 5-year survival rate was 95 and 89 per cent respectively; both were significantly greater than that of those with stage II, III and IV tumours (19·4 per cent). There was no significant advantage in 5-year survival following combined therapy.

Discussion

Although the resectability rate for oesophageal carcinoma has increased during the past 10 years, most series still describe poor surgical results[22]. The low rate of survival is due to the large proportion of advanced stage cases as a result of late diagnosis. In a previous review of the treatment of oesophageal cancer in Western countries, Muller *et al.*[23] reviewed 130 papers published between 1980 and 1988 involving surgery for oesophageal cancer in over 75000 patients. The overall mortality rate following oesophagectomy was 11 per cent. Survival rates for patients undergoing resection were 56 per cent for the first year, 34 per cent for the second year and 20 per cent for the fifth year. In a previous review of the surgical treatment of oesophageal cancer in China between 1940 and 1979, Wu *et al.*[24] reported an overall 5-year survival rate of 35 per cent. In the present review of Chinese language publications between 1980 and 1994, the 5-year survival rate following surgery was 28·1 per cent. Despite the surgical advances of the past 10 years, there has been no improvement in the prognosis of patients with oesophageal cancer.

To improve results of therapy for oesophageal carcinoma it is necessary to increase the rate of detection of early cases. Chinese experience with early detection by means of cytology screening programmes for oesophageal cancer demonstrates that patients with early tumours limited to the mucosa, not even evident on barium swallow, can be treated with a greater than 85 per cent 5-year survival rate by oesophageal stripping alone[25]. However, several criteria must be met for mass screening of a malignant disease before it can be proven efficacious.

Experience has shown that the technique of abrasive cytology is a simple and efficient procedure for the diagnosis of early carcinoma of the oesophagus. This technique has been adopted as an important diagnostic tool in most thoracic and oncology clinics.

The prognosis of patients with oesophageal carcinoma is related to the stage of the disease at presentation. In stage 0 and stage I disease, excellent long-term survival and even cure may be achieved by surgical treatment alone. In contrast, spread of disease beyond the mucosa into the oesophageal wall (stage II) or beyond (stage III) is associated with a marked reduction in patient survival.

Controversy continues over the most effective means to treat carcinoma of the oesophagus[26,27]. Despite recent advances, the results of surgery alone in advanced disease remain undeniably disappointing. Combining chemotherapy or radiotherapy with surgery has had little effect on operative morbidity and mortality rates. The present study suggests that preoperative radiotherapy alone does not increase resectability or long-term survival rates. Surgical therapy continues to be the cornerstone of nearly all treatment protocols, and is the only consistently effective modality for achieving substantial palliation and survival for these patients.

This review, like others, has shown that oesophageal carcinoma remains a disease with a dismal prognosis worldwide. In the absence of a major therapeutic advance, surgery remains the treatment of choice. Adjuvant chemoradiotherapy has yet to be proven beneficial. Mass screening programmes may be the only hope of improving results and may be suited to areas such as North China where there is a high incidence of oesophageal carcinoma.

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Short note

Surgery as a 'last resort' option for active variceal bleeding further complicated by iatrogenic oesophageal perforation

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Despite the advent of transjugular intrahepatic portosystemic stent shunting (TIPSS)[1,2] for variceal bleeding and the wide use of injection sclerotherapy, combined with other medical therapies, patients with active variceal bleeding not responding to endoscopic or radiological therapies are still referred to surgeons. The emergency surgical strategy adopted for five patients referred when emergency TIPSS was still under prospective evaluation is described.

Patients and methods

Between 1988 and 1993, patients initially treated on site for bleeding varices (approximately 20 per year) had their bleeding medically controlled and underwent elective shunting procedures, when indicated. By comparison five patients (three men and two women aged 53–80 years) were referred urgently from other institutions because of continued acute variceal bleeding despite the initiation of conventional treatment. All five patients (two with alcoholic and three with chronic hepatitic cirrhosis) had Child grade C and stage II hepatic encephalopathy. Four patients were referred in the era when TIPSS was still a technique under scrutiny, explaining why the procedure was attempted in only one patient from this small group (his portal vein was patent). Another patient with cirrhosis due to chronic hepatitis plus hepatocarcinoma underwent angiography, which showed portal vein thrombosis. Before operation none of these patients was suspected as having oesophageal perforation on clinical or radiological grounds.

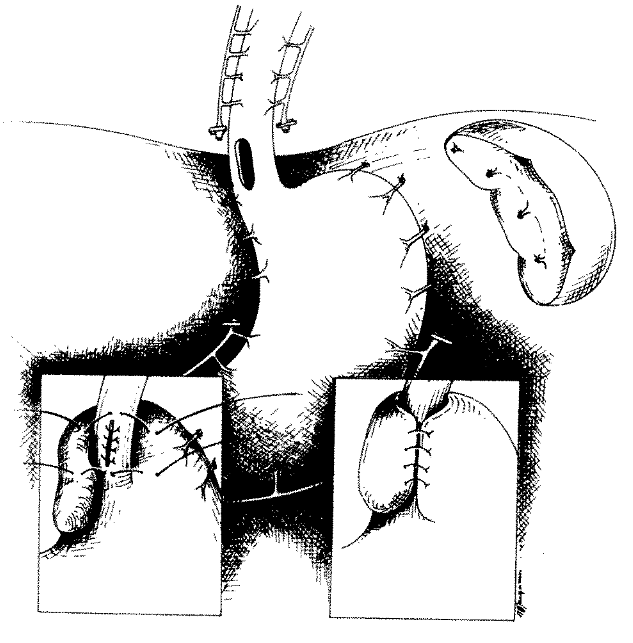

Fig. 1 Selective devascularization of the upper two-thirds of the stomach and the lower oesophagus, together with splenectomy. Left inset: Closure of the perforation and wrapping of the gastric wall around the abdominal oesophagus. Right inset: 360° fundoplication covering the area of oesophageal perforation

These patients had hepatic encephalopathy, so it was decided to perform selective devascularization[3] of the upper stomach and lower 8 cm of the oesophagus, together with splenectomy but without oesophageal transection. Initial exploration revealed perforation (range 0·5–2·5 cm in length) of the right anterior side of the abdominal portion of the oesophagus in four patients, probably related to sclerotherapy. In addition to the selective devascularization and closure of the oesophageal perforation (*Fig. 1*, left inset), a complete 360° fundoplication completed the procedure (*Fig. 1*, right inset) in order to cover and reinforce the area of oesophageal repair.

Results

Operative morbidity and mortality

The patient, who underwent an unsuccessful TIPSS procedure, died on the tenth postoperative day from multiple organ failure resulting from prolonged hypotension. Hospital stay for the four other patients ranged from 10 to 18 days. A 53-year-old woman with chronic obstructive pulmonary disease died 2 months after operation from acute respiratory distress syndrome. She had no recurrent bleeding from oesophageal varices. The postoperative Gastrografin (meglucamine ditrizoate; Schering, Berlin, Germany) swallow study performed in four patients was normal.

Long-term survival

One brief episode of recurrent bleeding occurred in the patient with hepatotocarcinoma 3 months later. She survived for 21 months. A 66-year-old patient with chronic hepatitic cirrhosis and a 64-year-old patient with alcoholic cirrhosis survived for 23 and 36 months respectively, without rebleeding. Endoscopy performed at 6 and 12 months demonstrated disappearance or regression of varices in these patients.

Discussion

Nowadays endoscopic sclerotherapy is the major treatment option for variceal bleeding. TIPSS is another promising technique, especially for patients who are reasonable candidates for liver transplantation. However, 20 per cent of patients still bleed or will rebleed during the first year after TIPSS[1,2], but the limited supply of

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organs for transplantation is an obvious restricting factor. If modern treatments fail or are unavailable, the burden of decision making and the choice of a 'last resort' operation will be shifted to the surgeon. The remaining alternatives are surgical portosystemic shunting or devascularization procedures.

The most alarming feature of this report is that four of the five patients had associated perforation of the abdominal portion of the oesophagus. This may be due to the sclerotherapy, to the fact that at least three patients were referred with an inflated Linton tube in place, or to the efforts of vomiting or retching causing laceration or rupture of the lower oesophagus.

Fundoplication was an easy way to bring a local tissue flap over the oesophageal repair. Another speculative benefit of fundoplication was constriction of the gastro-oesophageal junction, causing a decreased venous pressure in the remaining superior oesophageal veins above the level of the fundoplication[4,5]. The results of this 'last resort' strategy in terms of survival and control of bleeding are encouraging.

Acknowledgements

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Short note

Splenic irradiation for the treatment of hypersplenism from congestive splenomegaly

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Untreated hypersplenism carries a 5-year survival rate of only 50 per cent[1]. Hypersplenism can be treated by splenectomy or partial splenic embolization. The latter procedure can cause severe pain and serious complications have been reported with an immediate mortality rate of 12 per cent[2]. This was a study of splenic irradiation as an alternative treatment for hypersplenism due to portal hypertension from liver cirrhosis.

Patients and methods

The study was carried out prospectively on eight patients at Kasr El Aini Hospital between 1991 and 1995. There were five men and three women with a mean age of 38 (range 23–55) years. All had congestive splenomegaly due to liver cirrhosis, five had both ascites and oedema of the lower limbs, and three had suffered haematemesis. Mean portal vein diameter was 17 (range 14–21) mm on abdominal ultrasonography. Splenic size was determined before and after radiotherapy by ultrasonography[3].

All patients had a reduction of one or more haematological parameters, six had a hypercellular and two normocellular bone marrow. Chromium-51 uptake showed an increased rate of red cell sequestration in the spleen. Renal function was normal in all but one patient. All were high risk for surgery.

The spleen was irradiated using a cobalt-60 teletherapy unit, utilizing solely an anterior oblique field sufficient to cover the palpable spleen. An oblique field was used to avoid renal irradiation. Portal size was 200–300 cm^2. The source–skin distance was 80 cm. Dose range was from 50 to 150 cGy per sitting. Haematological parameters were estimated repeatedly during the radiotherapy and further sessions were deferred if the total white blood cell count fell below 2000 per mm^3.

Results

Two patients achieved a complete haematological response with return of all blood parameters to normal or near-normal values (*Table 1*). Three patients had at least 25 per cent improvement in one or more parameters (partial response). Splenic irradiation did not have a consistent effect on the various blood elements. Leucopaenia was corrected or improved in five patients, anaemia in three and thrombocytopaenia in three patients. The haematological response became apparent in responders within 4 weeks of irradiation but bore no relationship to the dose used. No Howell–Jolly bodies were detected in the final postirradiation smears indicating that some splenic function was retained.

Splenic cross-sectional area and size (taken as area multiplied by greatest anteroposterior diameter) decreased in all seven patients who completed the course of radiotherapy but did not correlate with the haematological response.

Renal function was not affected. All patients complained of chronic, dragging splenic pain before treatment which was relieved by radiotherapy.

In follow-up ranging from 3 to 43 months, no patient developed hypertension or radiation pneumonitis. There were two deaths from hepatic failure, one following splenectomy elsewhere. Neither death could be attributed to the radiotherapy.

Table 1 Response to radiotherapy for hypersplenism

	Splenic dimensions after irradiation*									
Patient no.	Length (cm)	Width (cm)	Depth (cm)	Diagonal breadth† (cm)	Cross-sectional area‡	Percentage decrease in cross-sectional area	Total cobalt dose (cGy)	Follow-up (months)	Haematological response	Relief of splenic pain
1	16 (20)	8 (10)	13 (14)	12 (15)	106 (163)	35	975	43	Partial	+
2	18 (21)	6 (10)	11 (14)	12 (16)	114 (182)	37	1350	38	Complete	+
3	20 (22)	14 (15)	18 (19)	15 (17)	186 (229)	19	2300	39	None	+
4	24 (26)	11 (12)	16 (18)	18 (18)	244 (263)	7	800	3	Partial	+
5	20 (23)	7 (9)	15 (16)	10 (12)	106 (144)	26	900	4	Complete	+
6	17 (21)	9 (11)	14 (14)	8 (11)	77 (129)	40	1900	4	None	+
7	18 (20)	10 (12)	14 (14)	11 (12)	117 (130)	10	300	5	None	+
8	(22)	(12)	(14)	(14)	(175)§		225§	—	Partial	+
Mean					136 (177)	25	1218	19		

*Values in parentheses are dimensions before irradiation. †Maximum diameter in the coronal plane lying at 45° to both the transverse and longitudinal diameters. ‡Cross-sectional area = diagonal × ($\sqrt{\text{length}^2+\text{width}^2}$)/2. §Not included in mean value; the course of splenic irradiation was interrupted by splenectomy elsewhere and the patient died from acute cholangitis

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Discussion

Hypersplenism occurs secondary to splenic congestion with intrasplenic sequestration and destruction of erythrocytes, leucocytes and platelets resulting in anaemia, leucopaenia and thrombocytopaenia. The usual treatment is splenectomy, although splenic embolization is an effective alternative.

The radioresponsiveness of the spleen is comparable to that of lymph nodes. Studies with chromium-51 indicate that there is decreased red cell breakdown and increased red cell survival following splenic irradiation for chronic leukaemia[4]. An increase in haemoglobin level of at least 2 g/dl occurred in 25 per cent of patients with leukaemia after radiotherapy[5].

This study assessed splenic irradiation as a non-invasive treatment for hypersplenism due to congestive splenomegaly from portal hypertension. Routine splenic irradiation is through anterior and posterior opposing fields weighted 3:2 from behind. These fields expose the kidney to irradiation. The present study solely used an anterior oblique field, thus avoiding renal irradiation.

The dose of splenic irradiation ranged from 50 to 150 cGy per sitting. The frequency of the sessions was guided by the response of the white cell count. The total cobalt dose did not exceed 2000 cGy in responders. This is the maximum dose suggested for further study. Two of the eight patients achieved a complete haematological response and three a partial response. There was no correlation between response and change in spleen size. There were no major early or late complications and the two late deaths were not attributable to radiotherapy. Chronic dragging splenic pain was relieved in all patients, an added advantage over portal splenic embolization. This safe, well tolerated treatment warrants further study.

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Long-term results of the Angelchik prosthesis for gastro-oesophageal reflux

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Introduction Between 1982 and 1989, 46 patients had insertion of an Angelchik prosthesis for gastro-oesophageal reflux. Eleven patients (24 per cent) subsequently had the prosthesis removed, all but one for intractable dysphagia.

Methods Thirty-six of the original patients were followed by questionnaire, and 32 of these had a barium marshmallow swallow investigation.

Results A high proportion of patients (20 of 26) with a prosthesis *in situ* had symptoms of dysphagia. On objective evaluation by marshmallow swallow, the transit time was significantly slower than that of an age-matched control group ($P < 0{\cdot}01$), but showed no significant deterioration with time compared with previous postinsertion studies.

Conclusion The Angelchik prosthesis causes long-term dysphagia in a high proportion of patients, severe enough in one-quarter to necessitate its removal. Its continued use cannot, therefore, be recommended.

In 1979 Angelchik and Cohen[1] described a silicone-containing halter-shaped elastomer shell which could be sited around the lower oesophagus via the transabdominal route for the control of reflux symptoms – the Angelchik prosthesis[1]. Since then, at least 25 000 such prostheses have been inserted worldwide[2].

Up to 150 complications have been documented following insertion of the Angelchik prosthesis[3]. The commonest include recurrent gastro-oesophageal reflux, erosion into the stomach, 'gas bloat' syndrome, migration into the thorax and dysphagia[4–12]. The aim of this paper is to report the long-term (5–10 years) follow-up of all patients who had an Angelchik prosthesis inserted at the Queen's Medical Centre, Nottingham.

Patients and methods

Between October 1982 and November 1989, 46 patients underwent insertion of an Angelchik prosthesis for gastro-oesophageal reflux refractory to long-term medical management. There were 30 men and 16 women (mean age 53 (range 21–72) years). The prostheses were inserted according to the manufacturer's instructions by five different surgeons of consultant, senior registrar or registrar status. All patients underwent preoperative and postoperative upper gastrointestinal endoscopy, oesophageal manometry, acid reflux provocation tests and 24-h pH monitoring. These results have been documented previously[5]. In addition, 36 patients had a marshmallow swallow investigation within 3 months of operation to document oesophageal transit times, and the results were found to correlate well with solid food dysphagia[6].

Of the 46 patients, two had died from unrelated causes; some 36 were traceable and agreed to further investigation. The mean follow-up since operation was 102 (range 53–134) months.

All 36 patients completed a questionnaire to assess symptoms of dysphagia, heartburn and regurgitation, and to document current medication. In addition, oesophageal transit was measured by means of a barium-labelled marshmallow swallow in 32 patients, as described previously[6]. Eleven subjects (five men and six women of mean age 48 (range 22–67) years) with no previous gastrointestinal symptoms were used as a control group for the marshmallow swallows.

Local ethical committee approval was obtained for the study.

Results

Eleven of the original 46 patients (24 per cent) have to date had the Angelchik prosthesis removed. In six cases this was for intractable dysphagia, with no displacement of the prosthesis. A further three patients had dysphagia secondary to rotation or displacement of the prosthesis within the abdomen. Intrathoracic migration of the prosthesis accounted for removal in the remaining two cases. In one this caused dysphagia, and in the other severe reflux symptoms. The interval between insertion and removal varied between 1 and 109 months (*Fig. 1*).

The 36 patients who completed the questionnaire were assessed in three groups: those who still had an Angelchik prosthesis *in situ* (26 patients), those who had a Nissen fundoplication following removal of the prosthesis (six) and those who had the prosthesis removed with no other procedure performed (four).

Twenty of the 26 patients with the prosthesis *in situ* reported dysphagia. Control of symptomatic regurgitation and heartburn was reasonable, with 19 and 15 respectively suffering neither symptom. Five of the six patients who had undergone removal followed by Nissen fundoplication had problems with dysphagia; only one patient in this group claimed never to suffer regurgitation or heartburn. None of the patients who had removal of the Angelchik prosthesis without a further procedure admitted to any dysphagia or heartburn, although two suffered occasional regurgitation.

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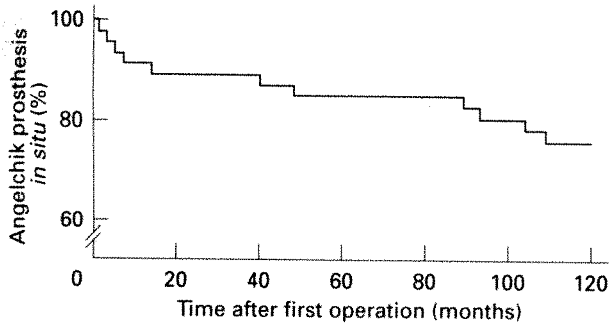

Fig. 1 Rate of removal of the Angelchik prosthesis in 46 patients

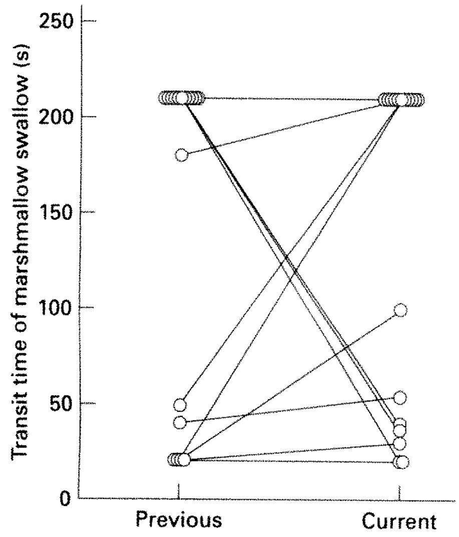

Fig. 2 Marshmallow transit time immediately after operation, compared with current values in patients with an Angelchik prosthesis *in situ*. The interval between investigations was 5 years or more. Note that in eight patients the transit time was greater than 210 s on both occasions

Of the patients with an Angelchik prosthesis still *in situ*, four were receiving antireflux therapy. Three of the six patients who had subsequent fundoplication, and two of the four who had removal of the prosthesis alone, were taking medication.

Of the 36 patients who completed a questionnaire, 32 consented to have a marshmallow swallow; in 27 of these a marshmallow swallow had also been carried out in the immediate postoperative period. Paired data were available for 18 patients with an Angelchik prosthesis *in situ*. All marshmallow swallows were done in a 1-month interval, a mean of 100 (range 54–120) months after the postoperative examination. When the immediate postoperative results were compared with the current figures, no significant difference was found (*Fig. 2*). However, when compared with the results for the control subjects, the patients with an Angelchik prosthesis *in situ* had significantly prolonged marshmallow transit times (median 41 (range 16 to more than 210) s *versus* 20 (range 14–32) s in controls; $P < 0{\cdot}01$, Mann–Whitney *U* test).

Discussion

There is little information regarding the long-term efficacy of the Angelchik prosthesis. The mean duration between operation and last assessment in these patients was 102 months, the longest follow-up in any series to date. Prospective randomized controlled trials have been published comparing the Angelchik prosthesis and Nissen fundoplication. Hill *et al.*[13] found that, at a mean follow-up of 84 months, both treatment options provided lasting control of gastro-oesophageal reflux, but that the Angelchik prosthesis required removal in three of 30 patients. Seventeen of the original 30 patients randomized to receive an Angelchik prosthesis suffered transient dysphagia. Hill *et al.*[13] also reported an absence of prosthesis-related complications beyond 12 months after insertion.

Kmiot *et al.*[14] randomized 50 patients to receive either an Angelchik prosthesis or Nissen fundoplication. This study was analysed early, and subsequently discontinued because of a subjective impression that the prosthesis group had a worse outcome. Initial results revealed that persistent dysphagia occurred in five patients, and required removal of the prosthesis in three.

Another randomized trial involving 48 patients[15] showed that 21 of 25 patients in the Angelchik group had achieved Visick grade 1–2 at the 4–6 years follow-up, compared with 18 of 23 in the Nissen fundoplication group. A further trial[2] showed that both procedures were equally effective at controlling reflux, but that 10 per cent of the Angelchik prostheses required removal.

Dysphagia is one of the most troublesome postoperative symptoms after insertion of the Angelchik prosthesis. A variety of causes has been proposed, including fibrous capsule formation, the mechanical effect of the prosthesis, and excessive approximation of the margins of the right crus[16]. Gear *et al.*[17] reported early dysphagia in 38 per cent of patients, but noted that resolution occurred in all but two within a few months. Similar values were obtained by Stuart and co-workers[2], and were reported in Angelchik and Cohen's original article[1]. Conversely, Starling *et al.*[18] did not discover significant postoperative dysphagia in the 6 months following operation. Wale and colleagues[19] found that 33 per cent of patients had mild dysphagia, and a further 12 per cent had moderate or severe symptoms after 12 months.

In this study 20 of the 26 patients with an Angelchik prosthesis still *in situ* reported dysphagia and, compared with controls, there was a significant delay in marshmallow transit time. However, there was no significant deterioration from the transit time observed in the immediate postoperative period when the paired marshmallow data were evaluated. Of six patients who had removal of the Angelchik prosthesis and subsequent floppy Nissen fundoplication as described by Donahue *et al.*[20], five admitted to occasional dysphagia. Technical difficulty in performing the operation after removal of the prosthesis may have accounted for these poor results. No dysphagia was found in patients who had removal of the prosthesis and no antireflux procedure performed.

These results confirm that the Angelchik prosthesis causes chronic dysphagia, sufficiently severe in a proportion of cases to warrant removal. The present removal rate (24 per cent) is the highest reported, other studies documenting rates between 5 and 17 per cent[2,19,21–23]. This may be a result of the length of follow-up: removal rates were found to be cumulative. It is of interest that the paired marshmallow swallows showed no significant deterioration with time. This may reflect a more favourable process in patients who did not require removal of the prosthesis, or that removal was necessitated by increasing intolerance of a stable situation.

In summary, the Angelchik prosthesis provides good long-term subjective control of gastro-oesophageal reflux but is associated with significant dysphagia. In a high proportion of cases this is severe enough to necessitate removal, and the subsequent results of revision antireflux surgery are not ideal. Based on these findings, it is difficult to recommend continued use of the Angelchik prosthesis.

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Surgical workshop

Endoscopic stenting for recurrent malignant gastric outlet obstruction

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Malignant gastric outlet obstruction causes significant morbidity. Intractable vomiting, poor nutrition, electrolyte imbalance, oesophagitis and dehydration may occur. Treatment poses a dilemma for the surgeon. In those with benign disease or malignant disease with a reasonable prognosis, a surgical drainage procedure is the treatment of choice. In patients with advanced recurrent disease where the short-term prognosis is poor, however, a laparotomy may be difficult to justify. A straightforward endoscopic technique for the relief of outlet obstruction is presented.

Surgical technique

A 79-year-old woman presented with weight loss and intractable vomiting 1 year after a partial gastrectomy with Roux-en-Y gastrojejunostomy for carcinoma of the gastric antrum. The tumour was a moderately well differentiated adenocarcinoma extending on to the serosa and tumour was found in all lymph nodes sampled but resection margins were clear. A barium meal showed complete hold up of contrast just distal to the gastrojejunal anastomosis (*Fig. 1*). Gastroscopy with a view to laser therapy revealed a tortuous stricture at the gastric outlet due to extrinsic compression by tumour. A further gastroscopy was performed and the endoscope negotiated through the stricture, allowing a guidewire to be passed. Under fluoroscopic control, a 7-cm, 21-mm internal diameter, covered, expandable metal stent (Schneider Wallstents, Bulach, Switzerland) was passed over the guidewire through the stricture, and released. This did not pass through the whole length of the stricture and a second stent was inserted to overlap with the first. Subsequent Gastrografin swallow (Schering, Berlin, Germany) demonstrated free flow of contrast into the distal small bowel (*Fig. 2*). The patient's symptoms resolved and she was allowed home. She was able to tolerate oral fluids and a soft diet until her death 5 weeks later.

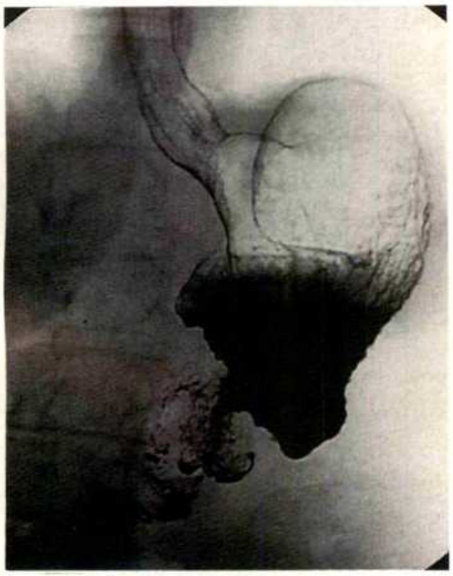

Fig. 1 Barium meal showing complete hold up of contrast at the gastrojejunal anastomosis

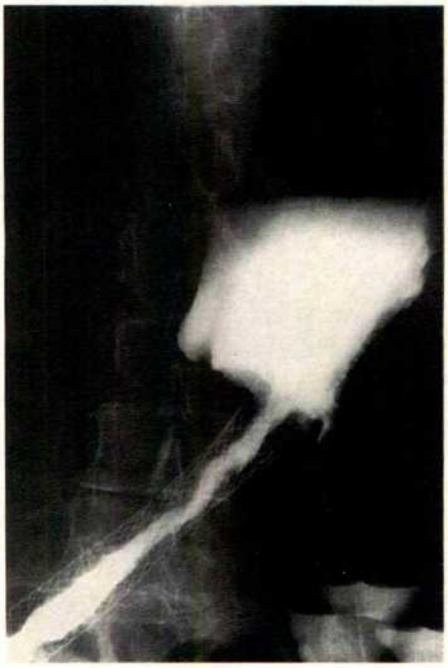

Fig. 2 Gastrografin swallow showing free flow of contrast from the stomach through the stent into the small bowel

Discussion

Expandable metal stents have been used with good effect in patients with advanced oesophageal carcinoma[1]. Surgery provides effective treatment for gastric outlet obstruction but when there is recurrent disease, a poor prognosis and a weak patient laparotomy may be inappropriate.

Other treatment modalities include endoluminal irradiation, laser ablation or chemical injection[2,3], but the use of these techniques depends largely on the presence of exophytic tumour. Several treatments may be required and there may be significant side-effects.

Expandable metal stents have a very low complication rate when used in the oesophagus[1]. Malposition on insertion can be compensated for by the use of a second overlapping stent. Bolus obstruction is a potential complication, but can be largely avoided by careful patient education[4].

Cost is a major consideration, especially when a single stent costs approximately £800. This procedure was carried out under sedation only and with minimal patient care afterwards. The patient was discharged 48 h after the stent was placed.

Compared with the many complications associated with surgery in these patients, this technique offers simple and effective palliation for a difficult problem.

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Short note

Influence of tumour penetration on period of death after gastric cancer surgery

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The initial 3 years have been considered the highest risk period for occurrence of cancer-related death after resection of gastric cancer[1–4]. However, death from recurrence may occur even 4 years after surgery. This retrospective study was undertaken to examine the influence of tumour penetration into the gastric wall on the period of risk of death from recurrent gastric cancer.

Patients and methods

The case notes of 871 patients with gastric cancer who had undergone gastric resection during the 22 years from 1 January 1974 to 31 December 1995 were reviewed. Of these 871 patients, 476 had a pT_1 tumour (invasion of the mucosa or submucosa) or a pT_2 tumour (invasion of the muscularis propria or subserosa), and 395 had a pT_3 tumour (penetration of the serosa and visceral peritoneum) or pT_4 tumour (invasion of adjacent structures). Each cancer-related death was plotted over the 10 years following surgery. The cumulative crude survival rate was calculated by the Kaplan–Meier method. Differences in the number of cancer-related deaths in each period between patients with a pT_1 or pT_2 tumour and those with a pT_3 or pT_4 tumour were evaluated by the χ^2 test.

Results

There were 45 cancer-related deaths in patients with a pT_1 or pT_2 tumour, and 195 cancer-related deaths in patients with a pT_3 or pT_4 tumour. In patients with a pT_3 or pT_4 tumour, 181 deaths (93 per cent) occurred in the initial 3 years, while in those with a pT_1 or pT_2 tumour, 29 of 45 deaths occurred in the same period. The cancer-related mortality rate in the initial 3 years was significantly higher in patients with a pT_3 or pT_4 tumour ($\chi^2 = 34{\cdot}35$, 6 d.f., $P < 0{\cdot}005$). Cancer-related deaths continued to occur in patients with a pT_1 or pT_2 tumour, even 4 years after surgery. Conversely, late cancer-related death was rare in patients with a pT_3 or pT_4 tumour. The slow reduction in the survival of patients with a pT_1 or pT_2 tumour reflects these results (*Table 1*). Thirty-one of 45 deaths in patients with a pT_1 or pT_2 tumour were associated with haematogenous dissemination, while 160 deaths (82 per cent) in patients with a pT_3 or pT_4 tumour were caused by peritoneal recurrence.

Table 1 Number of deaths and survival rate after surgery

	Year after surgery										
	1	2	3	4	5	6	7	8	9	10	>10
No. of deaths											
pT_1 or pT_2 tumour	18 (40)	5 (11)	6 (13)	3 (7)	3 (7)	4 (9)	2 (4)	0 (0)	2 (4)	0 (0)	2 (4)
pT_3 or pT_4 tumour	104 (53·3)	56 (28·7)	21 (10·8)	2 (1·0)	6 (3·1)	1 (0·5)	1 (0·5)	1 (0·5)	2 (1·0)	1 (0·5)	0 (0)
pT_1 or pT_2 tumour											
Survival rate (%)	96·0	94·6	92·8	91·3	90·0	87·6	86·2	86·2	83·0	83·0	
No. of patients at risk	390	329	265	226	181	135	94	59	37	18	
pT_3 or pT_4 tumour											
Survival rate (%)	70·1	50·8	42·2	41·1	36·8	35·9	34·4	32·7	28·1	24·5	
No. of patients at risk	217	138	82	68	43	33	25	16	11	5	

Values in parentheses are percentages. Some 103 patients with a pT_1 or pT_2 tumour, and 60 patients with a pT_3 or pT_4 tumour, were followed up for less than 5 years

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Discussion

Determination of the risk period for cancer-related death after surgery is important in the management of patients with gastric cancer. The initial 3 years after surgery has been generally regarded as the highest risk period for cancer-related death. However, the present study demonstrates that the risk period for cancer-related death is influenced by the depth of cancer penetration into the stomach wall. The most important finding in the present study is that cancer-related deaths continued to occur even 4 years after surgery in patients with a pT_1 or pT_2 tumour. This might be explained by the authors' previous report that the majority of cancer-related deaths in patients with a pT_1 or pT_2 tumour were associated with blood-borne metastases from intestinal-type gastric carcinomas, which may appear later after surgery[5]. In contrast, peritoneal dissemination, which was often seen in patients with a pT_3 or pT_4 tumour, appeared shortly after surgery. These findings provide helpful information in the management of patients after resection of gastric cancer.

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Short note

Disappointing long-term results of laparoscopic adjustable silicone gastric banding

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In a recent paper[1] a new technique for treatment of morbid obesity, laparoscopic adjustable silicone gastric banding, was described. The long-term results of this technique are presented.

Patients and methods

Between June 1993 and February 1995, 15 morbidly obese patients were treated by laparoscopic adjustable silicone gastric banding. There were two men and 13 women, with a mean age of 33 (range 19–50) years and mean body-weight 185·4 (range 172–225·5) per cent of ideal.

The surgical technique has been described previously[1]. In the first seven patients a silicone inflatable band already used in open surgery was used (Bioenterics, Carpinteria, California, USA); in the last eight patients a new band (Lap-band) (Bioenterics), specifically designed for laparoscopic surgery, was adopted. A 25-ml pouch was constructed in the first eight patients and a 15-ml pouch in the others. Water-soluble contrast radiography was performed on the third postoperative day in all patients. The patients were discharged 5–7 days after operation.

Results

There were no operative deaths. The postoperative course was uneventful in all patients and was characterized by all the advantages of laparoscopic surgery in terms of minimum pain and discomfort; no patient in this series required opioids, while these drugs were routinely administered for 24–48 h in patients operated by laparotomy. The mean postoperative stay was 7·2 (range 5–14) days.

At a mean follow-up of 20 (range 12–30) months, the excess weight loss, expressed as a percentage of preoperative overweight, was 35 per cent at 3 months, 49 per cent at 6 months, 66 per cent at 1 year and 67 per cent at 2 years.

Nine patients presented with sudden food intolerance following successful weight loss at mean 12·2 (range 2–28) months after the intervention. In these patients radiological examination showed a large pouch dilatation with a distal dislocation of the band and a total functional stoma obstruction (*Fig. 1*). Endoscopy revealed oesophagitis due to severe vomiting, but a normal stomal appearance. In all nine patients desufflation of the band did not lead to any clinical or radiological improvement.

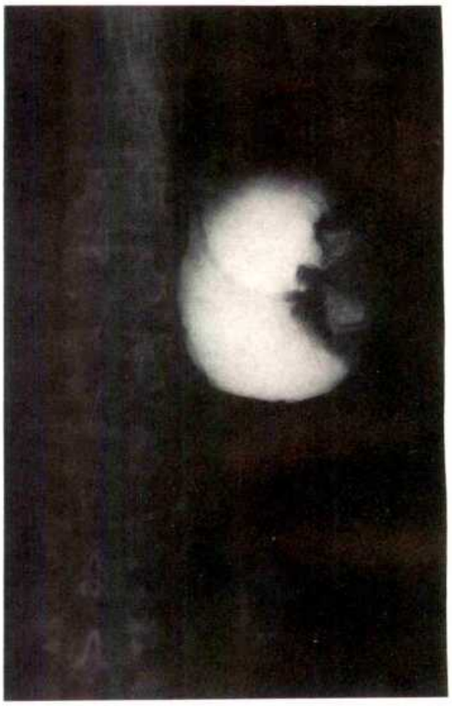

Fig. 1 Radiological control 13 months after laparoscopic adjustable silicone gastric banding showing wide pouch enlargement and severely delayed passage of contrast medium through the stoma

All nine patients with this functional stenosis were reoperated: three bands were removed, five patients underwent vertical banded gastroplasty (two laparoscopically) and one had gastric bypass. One additional patient with a small pouch was reoperated 9 months later for failure to lose weight and subsequently underwent vertical banded gastroplasty.

Five patients, one with a traditional band and four with the Lap-band, remain asymptomatic 12–27 months after surgery with a mean excess weight loss of 66·6 (range 57–80) per cent.

Discussion

The advantages of laparoscopic surgery in reducing respiratory distress, ileus, pain and incisional hernia represent a major benefit to morbidly obese patients. Therefore, after a 20-year experience of traditional bariatric surgery, the authors started using laparoscopic bariatric surgery in 1993. Because of its simplicity and effectiveness adjustable silicone gastric banding, as described by Kuzmak[2], was performed laparoscopically.

Early clinical results were excellent with no morbidity or deaths and an early discharge for all patients. Moreover, the excess weight loss was satisfactory: 35 per cent at 3 months, 66 per cent at 1 year and 67 per cent at 2 years. These results compare favourably with those reported by Kuzmak with the open technique[2]. Nevertheless, long-term failure occurred in ten of 15 patients because of pouch dilatation with functional stomal stenosis in nine patients and a failure to lose weight in one.

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Two mechanisms may explain functional stomal stenosis. Pouch overstretching because of excessive food intake was proposed by van Eerten *et al.*[3], and reduction of the pouch volume from 25 to 15 ml was suggested to prevent this complication. The present results were not significantly improved by reducing the pouch volume: five of eight developed stenosis in the 25-ml pouches and four of seven in the 15-ml pouches.

A second hypothesis was proposed by O'Brien and McMurrick[4]: a posterior gastric wall prolapse from below to above the band. The absence of posterior adhesions typical of the laparoscopic approach could possibly explain this high frequency of pouch enlargement. The use of antislippage sutures on the posterior gastric wall[5], or placement of a Marlex (C-R Bard, Billerica, Massachusetts, USA) bolster on the posterior gastric wall below the band[4], have recently been suggested.

As a consequence of such disappointing long-term results, the laparoscopic adjustable silicone gastric banding has been abandoned in favour of vertical banded gastroplasty by the laparoscopic approach.

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Surgical workshop

Laparoscopically-assisted total pharyngolaryngo-oesophagectomy

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Conventional total pharyngolaryngo-oesophagectomy (PLO), for postcricoid carcinoma, requires gastric mobilization via laparotomy with either thoracotomy or blind transhiatal dissection of the mediastinal oesophagus. Thoracoscopic approaches to the oesophagus have been developed to reduce postoperative morbidity[1].

A laparoscopic technique is described in which the stomach and mediastinal oesophagus are mobilized transabdominally with the benefits of minimally invasive abdominal surgery and removing the necessity for a thoracic wound.

Surgical technique

The initial stage involves conventional open total pharyngolaryngectomy with formation of an end tracheostomy. Blunt oesophageal dissection in the upper mediastinum is performed as far as the carina.

The second stage involves oesophagogastric mobilization. Ports are placed in the upper abdomen ensuring that instruments reach the level of the angle of Louis. A liver retractor is placed in a right flank port and working ports are located in the midline above the umbilicus (two) and in the left hypochondrium (two). Mobilization of the greater curve of the stomach is facilitated by gastric retraction with endoscopic Babcock forceps and elevation of the greater omentum with dissectors allowing identification of the gastroepiploic arcade. Omental and short gastric vessels are divided using the harmonic scalpel, clips and electrosurgical scissors or linear stapler and cutter loaded with a vascular cartridge (Endo-GIA; AutoSuture, Ascot, UK). The laparoscope is moved to the left hypochondrium for the pyloric dissection. Mobilization of the lesser curve is achieved as the lesser omentum is incised from the pylorus to the oesophageal hiatus preserving the right gastric artery. The left gastric pedicle is divided at its origin with either double Ligaclips (Ethicon, Edinburgh, UK) or the Endo-GIA stapler. Kocher's procedure is accomplished by downward retraction of the hepatic flexure allowing sharp dissection lateral to the second part of the duodenum which is swept to the left using a dissector.

The oesophageal hiatus is mobilized by upward dissection from the lesser curve and fundus on to the oesophageal hiatus by sharp and electrosurgical dissection. The vagi are divided and loose connective tissue swept back using blunt or aquadissection, freeing the oesophagus. Mobilization of the mediastinal oesophagus is continued through the hiatus under direct vision using blunt and sharp dissection. The oesophageal blood supply is divided between Ligaclips (*Fig. 1*) and the oesophagus is separated from the parietal pleura and fibrous pericardium. This is continued to the carina, becoming confluent with the dissection from above.

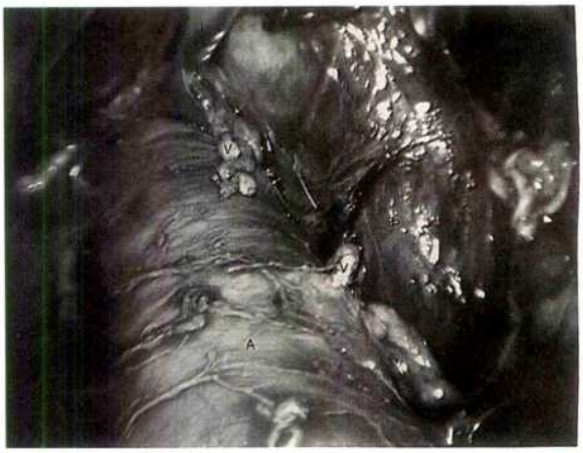

Fig. 1 Descending thoracic aorta (A) seen through the hiatus. O, oesophagus elevated by an instrument (I); P, left parietal pleura; V, oesophageal vessels clipped and ligated

Finally, the gastro-oesophageal segment is drawn into the neck by traction from above and laparoscopic manipulation from below. The pharyngolaryngo-oesophageal segment is excised and a pharyngogastric anastomosis performed at the base of the tongue.

Results

This technique has been used in three patients with a postcricoid carcinoma. In one case insufflation failure immediately before gastric transposition necessitated minilaparotomy after successful gastro–oesophageal mobilization. The other two patients required less than 4 units of perioperative blood, were sitting out within 24 h of discontinuing ventilation on the intensive therapy unit and had a postoperative stay of 29 and 17 days. Total operative times were 11 and 7 h.

Discussion

Total PLO for postcricoid carcinoma achieves acceptable cure and palliation. The 1- and 5-year survival rates are 50 and 30 per cent respectively; however, inpatient stay is over 30 days in 50 per cent of patients[2] and the operation is associated with significant morbidity and mortality rates[3]. Blind transhiatal oesophagectomy circumvents thoracotomy but carries its own risks of aortic bleeding, tracheal injury, pneumothorax or cardiac impairment[4]. Thoracoscopic oesophageal mobilization may reduce the morbidity of oesophagectomy and decrease hospitalization[1]. However, the pleural cavity is breached and still requires drainage. Reduced postoperative ventilation subsequent to this may reduce the benefits over conventional surgery[5].

Transhiatal laparoscopic oesophagectomy removes the necessity for a chest incision and has the potential benefits of a minimally invasive approach. The procedure only uses endoscopic techniques on normal tissue, minimizing the risk of port-site recurrence. Conventional oncological clearance is performed in the neck by direct surgery.

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Although not all surgeons will wish to adopt this laparoscopic approach, the present technique may benefit patients who require PLO and have suitable body habitus, provided that equipment, surgical expertise and operative time are available.

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Surgical workshop

Knot-free subcuticular suture

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Subcuticular sutures have largely replaced interrupted sutures for skin closure in general surgery. There are, however, a variety of techniques and materials used. Absorbable sutures have been shown to be as effective as non-absorbable sutures in the healing of abdominal wounds[1]. The avoidance of removal saves nursing time and discomfort for the patient, which can be distressing in children. Subcuticular knots may cause postoperative symptoms, and a technique to avoid these is described.

Surgical technique

The suture is introduced through the skin 1 cm proximal to the apex of the wound, exiting in the wound at the subcutaneous–dermal junction 4 mm distal to its apex. The needle is reintroduced in the subcuticular plane exactly at the apex, exiting 4 mm from the apex in that plane. The needle is passed through the loop created (*Fig 1*). Sufficient length to complete the closure is pulled through, and the suture is then locked by traction on the needle and countertraction on the distal end of the suture.

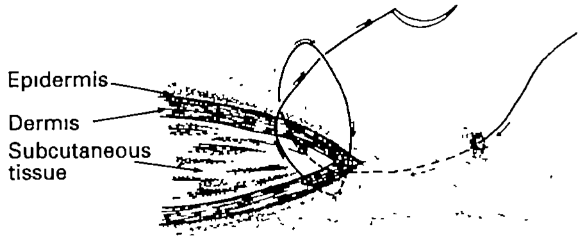

Fig. 1 Locking stitch at the start of the closure

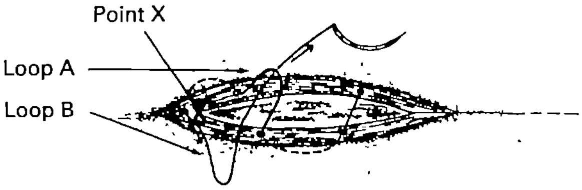

Fig. 2 The penultimate stitch and loops A and B

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The subcuticular suture is continued in the standard way. Locking the distal end is not as simple. The final bite enters 4 mm from the apex and exits exactly at the apex. A short loop is maintained from the penultimate stitch (loop A in *Fig. 2*) and the needle is passed under this loop. The suture is tightened by firmly pulling the suture between the finger and thumb of the left hand in the direction of the arrow on loop B in *Fig. 2*. This creates loop B but tightens loop A and closes the wound. Loop B is then pulled tight by traction on the needle in the direction of the second arrow in *Fig. 2*, to lock the suture. Finally, the needle enters the apex of the wound at the subcutaneous–dermal junction (point X in *Fig. 2*) and exits the skin 1 cm distal to the apex. Both ends are cut flush with the skin.

For lengthy wounds, two sutures can be used starting from opposite ends of the wound; they are joined at the midpoint with a buried knot.

Discussion

This technique has been effective in the hands of the author for skin closure in the operations commonly performed in a general surgical unit, over a period of 9 months. Other techniques have been described for securing absorbable subcuticular sutures[2,3]. This alternative method is simple and saves time. The usual suture used is 3/0 polyglactin 910 with a 22-mm curved cutting needle. For incisions less than 3 cm in length, as in laparoscopic port-site incisions, 4/0 polyglactin with a 16-mm needle is easier to use; 3/0 catgut is equally effective and may be used to close scrotal incisions. Polydioxanone sulphate has been found to be unsuitable as it provides insufficient tissue drag.

Acknowledgements

The author thanks Mr J. Mampilly for teaching him the basis of this technique and Julia Hillbourne for the illustrations.

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Surgical Infection Society of Europe Abstracts

The following abstracts were presented at the tenth annual meeting of the Surgical Infection Society of Europe held in Istanbul, Turkey between 29–30 May 1997.

Gene transfer with human interleukin 4 and 13 improves survival to lethal endotoxaemia in mice

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Anticytokine therapies have been unsuccessful in preventing mortality from Gram-negative bacteraemia in humans partly because of the failure to neutralize proinflammatory cytokines at the tissue level. To deliver tumour necrosis factor (TNF) inhibitors to organs directly, the authors employed human gene transfer. Thirty-six BALB/c mice (female 20–25 g) were injected intraperitoneally with 200 μg of either a pcD/hIL-4 or a pSRa/hIL-13 plasmid in cationic liposomes. Both pIL-4 messenger RNA (mRNA) and interleukin (IL)13 mRNA were detected by RT-PCR analysis in liver, spleen, kidney and lungs of the animals Subsequently, these 36 and 18 untreated animals were challenged with a LD_{100} dose of *Escherichia coli* lipopolysaccharide with D-GalN 18 mg per animal 48 h later

While gene transfer with hIL-4 reduced the serum TNF response to endotoxin from 113·1 pg/ml in untreated animals to 22·2 pg/ml at 90 min, human IL-13 gene transfer reduced serum TNF immunoactivity to 90 per cent (11·6 pg/ml; $P<0\cdot05$). Survival was improved by over 83 per cent in both treatment groups ($P<0\cdot001$).

These data demonstrate the anti-inflammatory actions of both IL-4 and IL-13 *in vivo*. It is also demonstrated that IL-13 displays a stronger TNF downregulation than IL-4 in this model. These experiments suggest that gene therapy is a promising option for the treatment of septic shock

Elective surgery induces an increase in circulating apoptotic neutrophils

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Neutrophils undergoing apoptosis are characterized by defects in microbicidal, phagocytic and chemotactic ability and are therefore ineffective in mediating an appropriate host defence response The authors examined systemic neutrophils in the immediate postoperative period for respiratory burst capacity, CD11b receptor expression and apoptosis

Patients undergoing colorectal surgery had whole blood taken at T_0, T_2, T_6, T_{12}, T_{18} and T_{24} h after operation This was analysed for neutrophil count, superoxide respiratory burst activity (RBA = neutrophil function) and CD11b/CD16 (markers of apoptosis) using flow cytometry. Apoptosis was further characterized with propidium iodide staining and subsequent flow cytometric analysis.

Mean(s.e.m) channel fluorescence

	T_0	T_2	T_6	T_{12}	T_{18}	T_{24}
CD11b	154(20)	166(31)	241(34)*	199(21)*	172(22)	161(21)
RBA	163(41)	152(41)	120(49)	93(45)*	153(69)	85(31)*
CD16	115(29)	120(10)	68(13)*	69(17)*	73(13)*	80(5)

*$P<0\cdot05$

Neutrophilia occurred between 6 and 12 h after operation. Neutrophil CD11b receptor expression was upregulated between 6 and 12 h after operation ($P<0\cdot05$). CD16 receptor expression was downregulated until 24 h after operation ($P<0\cdot05$). Superoxide RBA was also downregulated significantly 12 h after operation ($P<0\cdot05$). The postoperative neutrophil apoptotic rates were increased at 6 h relative to preoperative values.

Elective surgery resulted in a significant increase in systemic neutrophil programmed cell death, a finding that may also account for defective oxidant activity. These results demonstrate that injury programmes proinflammatory cells for early death and may represent a significant development in our understanding of postoperative sepsis.

Effect of different meshes on bacterial translocation

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It has been shown that implantation of intra-abdominal biomaterials promotes bacterial translocation (BT) This study determined whether mesh insertion promoted BT and if different mesh types made any difference.

Swiss albino mice were divided into group 1 (control), group 2 (polypropylene mesh (PP)), group 3 (polyglactin mesh (PC)) and group 4 (dura mater mesh (DM)). Laparotomies were performed with creation of an abdominal wall defect. In group 1, the defect was closed with 5/0 polyester. PP, PG and DM meshes were used to repair the defects in groups 2, 3 and 4 respectively. In the latter three groups, the intestines were in contact with the mesh. Samples from mesenteric lymph nodes, liver, spleen and caecum were obtained to evaluate BT 24 and 48 h after operation.

Each group had 12 to 17 animals for each time period. At 4 h the PP group showed increased BT compared to control and DM group animals ($P<0\cdot05$ and $P<0\cdot01$ respectively). At 24 h the PG group had increased BT compared with controls ($P<0\cdot05$), whereas both PG and PP groups had increased BT compared with the DM group ($P<0\cdot05$ for both). At 48 h both PG and PP groups had increased BT compared with the control group ($P<0\cdot05$ and $P<0\cdot001$ respectively) whereas the PP group also had increased BT compared with the DM group ($P<0\cdot001$). In the PG group there was a significant increase in BT at 24 h compared with 4 h ($P<0\cdot05$).

The use of prosthetic mesh led to an increased BT compared with DM mesh This effect might be attributable to its organic and physical nature.

Monocytic membrane CD14 expression and free endotoxin elimination of human mononuclear cells during sepsis

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The clinical presentation of Gram-negative sepsis, which is at least partly caused by endotoxin, is due to the activation of mediator cascades such as cytokines. It is generally accepted that the activation process of monocytic cytokine (MNC) production strongly depends on the expression of membrane CD14. Although the interaction of lipopolysaccharide (LPS) with membrane-bound receptors is well studied, little is known about cell-mediated LPS elimination. Eight patients with sepsis (Acute Physiology And Chronic Health Evaluation II score 12(2·4)), a patient with paroxysmal nocturnal haemoglobinuria (PNH) and nine healthy volunteers were enrolled in this study. The authors also examined pancreatic and colorectal cancer cell lines and hepatocytic cells as controls. Cells were incubated with 1 ng/ml of *Escherichia coli* LPS in FCS medium LPS levels of the supernatant were determined by a chromogenic modification of the limulus test at different time points. The supernatant levels of IL-1β, IL-6 and TNF-α were determined by enzyme-linked immunosorbent assay. The expression of monocytic CD14 was determined by FACScan analysis. To determine the FITC-LPS uptake to cells by FACScan analysis, cells were incubated with FITC-conjugated LPS for different time points.

Healthy MNCs eliminated the added LPS in a time- and cell number-dependent manner and the maximal neutralization was achieved after 2–4 h. MNCs from septic patients and a PNH patient with sepsis showed a similar time course as compared with healthy MNCs. However, a PNH patient in a stable state showed almost no LPS elimination. Pancreatic cells showed almost no cell-mediated LPS elimination. The LPS uptake to monocytes was detectable from 100 ng/ml FITC-LPS. The uptake of monocytes from patients with sepsis showed a nearly identical time course compared with that of healthy subjects. The expression of membrane CD14 of gated monocytes reduced from 95 per cent in healthy subjects to 28 per cent in patients with sepsis and 0 per cent in the patient with PNH ($P<0{\cdot}01$). There was a significant reduction of LPS-induced TNF-α release by MNCs derived from the patients with sepsis.

(1) Peripheral blood mononuclear cells may be involved in the endotoxin neutralizing capacity of human blood because exogenously added LPS was eliminated by MNCs depending on time and cell count.
(2) No correlation between the elimination capacity and the expression of membrane CD14 was found, at least in the septic state.
(3) Cell-based mechanisms of endotoxin clearance in the septic state are mediated by receptors other than CD14 and may be differentially regulated from the activation process of mononuclear cells

Improvement of survival from peritonitis by inhibition of cytokine production

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High-protein diets hasten mortality when given to animals with sustained untreated peritonitis because of an increased production of cytokines by the gut. CNI-1493 is a new drug that inhibits the production of tumour necrosis factor (TNF), interleukin (IL) 1, IL-6 and nitric oxide synthetase. It is beneficial in acute pancreatitis, cardiac allograft rejection and a short-term sepsis model using caecal ligation and puncture This study determined whether inhibition of cytokine production would be beneficial in a model of peritonitis which is 100 per cent fatal. Seven-day mini-osmotic pumps were filled with *Escherichia coli* and *Staphylococcus aureus* and implanted intraperitoneally in gastrostomized rats. Experimental groups received CNI-1493 5 mg/kg or 1 mg/kg intraperitoneally daily in divided doses from the time of pump implantation whereas controls received saline (13 per group). All animals were fed a 20 per cent protein liquid diet continuously by gastrostomy By 23 days all controls had died compared with 50–55 per cent of animals treated with CNI-1493.

CNI-1493, a drug that inhibits inflammatory cytokine production, significantly improved survival in rats with severe peritonitis that were fed high-protein diets.

Selective and non-selective nitric oxide synthase inhibition in early endotoxaemia: effects on hepatic morphology and function

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Endotoxin (lipopolysaccharide (LPS)) has profound effects on nitric oxide (NO) production, and controversies exist about whether these alterations are beneficial or deleterious. Non-selective inhibition of NO synthase seems to increase mortality, whereas inhibition of the inducible isoform (iNOS) so far appears positive. In a model of rat endotoxaemia the authors compared the early effects on hepatic morphology and function of selective (AE-ITU) and non-selective (L-NAME) NO inhibition. Two hours after the injection of LPS 5 mg/kg body-weight intraportally the rats were randomly assigned to three groups: group 1 (seven) had L-NAME 10 mg per kg body-weight, group 2 (six) AE-ITU 10 mg per kg body-weight and group 3 (seven) equal volumes of NaCl intraportally. Hepatic morphology was assessed with light (LM) and electron microscopic (EM) examination, hepatic function with arterial ketone body ratio, bile production, blood gases and liver enzymes.

Both antagonists reduced NO levels after 3 h. LM and EM examination revealed widespread destruction of liver tissue, without difference between the groups. The functional parameters consistently showed best values for the NaCl group, and worse values for the L-NAME group.

Inhibition of NOS in the early phases of endotoxaemia accentuates liver injury This includes suppression of the imminent iNOS induction.

Effect of aminoguanidine on vascular responsiveness of pulmonary and renal vascular beds in endotoxaemia

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The lungs and kidneys are the most commonly affected organs in Gram-negative sepsis. The involvement of nitric oxide (NO) in vascular responsiveness has been well demonstrated in experimental models of endotoxaemia.

The study investigated the effect of aminoguanidine and the selective inducible NO synthase (iNOS) inhibitor on the vascular responses in isolated perfused rat lung and kidney in endotoxaemia.

The rats were treated with an intraperitoneal injection of either lipopolysaccharide (LPS) 20 mg/kg or saline (control) 4 h before the study. The subgroups of the control and LPS groups were pretreated with aminoguanidine 20 mg/kg intraperitoneally. The vascular contractile response was evaluated in an isolated organ perfusion system to U-46619 (thromboxane A_2 mimetic agent) (3–30 nM) in the lung and phenylephrine (0·1–3 μM) in the kidney. The endothelium-dependent relaxation was evaluated as a response to acetylcholine in both lung (0·02–20 μg) and kidney (0·1–1000 μg).

In the isolated rat lung, contractile response to U-46619 was found to be attenuated by LPS pretreatment compared with the control group ($P<0{\cdot}05$). Acetylcholine-induced endothelium-dependent relaxation response was also impaired in the LPS group ($P<0{\cdot}05$). Aminoguanidine pretreatment restored not only the attenuated contractile response to U-46619 but also the impaired acetylcholine relaxation in the LPS group ($P<0{\cdot}05$). In isolated rat kidney, control contractile response to phenylephrine was not altered by LPS pretreatment. However, acetylcholine-induced relaxation was significantly attenuated in the LPS group ($P<0{\cdot}05$) Pretreatment with aminoguanidine prevented the impairment of this relaxation response ($P<0{\cdot}05$). Aminoguanidine pretreatment did not alter the contractile and relaxation responses in both lung and kidney preparations from the control group of rats

This study demonstrated that endotoxaemia leads to impaired contractile responsiveness in the pulmonary but not in the renal vascular bed. However, impairment of endothelial response was observed in both tissues. The prevention achieved by aminoguanidine indicates the role of iNOS induction and may offer a novel therapeutic approach

Organ injury and neutrophil sequestration are mediated differentially by C-X-C chemokines during faecal peritonitis

M. A. Mercer-Jones, D. Wickel, J. Peyton, M. Heinzelman, W. G. Cheadle, *University of Louisville and VAMC, USA*

Neutrophils (polymorphonuclear neutrophils (PMNs)) mediate organ injury after experimental peritonitis (caecal ligation and puncture (CLP)) and are an important peritoneal host defence. The murine PMN-specific (C-X-C) chemokines, KC and macrophage inflammatory protein (MIP) 2, upregulate CD18, increase respiratory burst and are potent chemoattractants.

Double 18-G CLP was performed on 18 Swiss Webster mice. At 3, 6 and 18 h, liver, lung and peritoneal leucocyte KC and MIP-2 messenger RNA (mRNA) expression was determined by polymerase chain reaction and protein was detected by enzyme-linked immunosorbent assay and immunohistochemistry. Mice (ten per group), at the time of CLP, were then injected intravenously with anti-MIP-2, anti-KC antibodies, control serum or underwent no procedure. At 6 h, peritoneal PMNs were counted, liver and lung assayed for myeloperoxidase (MPO) content, and serum for transaminases. To detect a survival benefit, CLP was performed at the time of anti-KC (18) or serum (18) injection.

Liver, lung and peritoneal leucocytes showed a progressive increase in MIP-2, KC mRNA and protein expression after CLP Early survival (24–48 h) was improved in anti-KC-treated mice ($P<0\cdot05$). Peritoneal neutrophil migration was reduced by anti-MIP-2 but not by anti-KC treatment.

	Liver MPO (U/g)	Lung MPO (U/g)	AST (U/ml)	ALT (U/ml)
Normal	0·36(0·02)	25·8(4·1)	47·5(5·2)	22·5(2·2)
Controls	2·99(1·1)	116·1(9·6)	210·7(15·5)	124·8(17·8)
Anti-KC	1·97(0·8)	96·9(10·9)	144·8(10·1)*	80·4(4·9)*
Anti-MIP-2	2·53(0·5)	80·5(12)*	192·6(24·8)	113(8·5)

Values are mean(s.e.m.). AST, aspartate aminotransferase, ALT, alanine aminotransferase, *$P<0\cdot05$, analysis of variance

While MIP-2 regulates lung and peritoneal neutrophil sequestration, KC regulates PMN-mediated hepatic injury without affecting liver PMN sequestration, perhaps by inducing PMN respiratory burst.

Effect of pentoxifylline in sepsis. Results of a double-blind, randomized, placebo-controlled study

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Pentoxifylline (POF) inhibits macrophage production of tumour necrosis factor (TNF) as a central mediator in sepsis. To evaluate the therapeutic effect of POF in patients with sepsis a prospective, randomized, double-blind, placebo-controlled study in two centres was performed.

Fifty-one patients were included and randomized to receive POF continuously (1 mg/kg body-weight per hour intravenously), or saline solution as placebo over 28 days, or until patients were discharged from the intensive care unit, or until they died. Bioactivity of TNF and interleukin (IL) 6, multiple organ failure (MOF) score according to Goris as well as organ function were determined at diagnosis, daily from day 1 to 7, and on days 10, 14, 17, 21, 24 and 28 after diagnosis of sepsis. There were no differences in patient characteristics at diagnosis, Acute Physiology And Chronic Health Evaluation (APACHE) II score (17(4) POF and 18(5) placebo), MOF score (10·5 *versus* 10·7) or organ function. At study entrance 23 of 27 patients in the POF group and 21 of 24 in the control group had septic shock. No adverse effects of POF treatment were observed

The 28-day mortality rate was eight of 27 in POF-treated patients and eight of 24 in the control group. Hospital mortality was 11 of 27 in the POF group and 13 of 24 in control patients. Serum concentrations of TNF and IL-6 were not significantly different throughout the evaluation. MOF score was lower in POF patients after day 4 compared with placebo-treated patients, and was significantly different on days 14 and 21 ($P<0\cdot05$). PaO_2/FiO_2 ratio was significantly improved in POF patients from day 10 (266(132)) to day 21 (346(142)) compared with the placebo group (201(161) *versus* 221(112), $P<0.05$ and $P<0\cdot01$ on days 14 and 17). Pressure-adjusted heart rate (HR × central venous pressure/mean arterial pressure) was significantly improved between days 6 and 10 ($P<0\cdot05$) in patients treated with POF compared with the control group.

Continuous intravenous administration of POF beneficially influenced organ function in patients with sepsis without adverse effects. A multicentre trial is needed to evaluate the efficacy in improving organ function and outcome of patients with sepsis

Benefits of early enteral nutrition in acute pancreatitis

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Total enteral nutrition (TEN) significantly improves septic morbidity in patients with major trauma and burns when compared with total parenteral nutrition (TPN). Poor outcome in acute pancreatitis is associated with a high incidence of systemic inflammatory response syndrome (SIRS) and sepsis; thus, TEN may have a therapeutic rationale in acute pancreatitis. Glasgow score, Acute Physiology And Chronic Health Evaluation (APACHE) II score, computed tomography (CT) score, C-reactive protein (CRP), serum immunoglobulin (Ig) M antiendotoxin (EndoCAb) antibodies and total antioxidant capacity (TAC) were determined on admission in 34 patients with acute pancreatitis. Patients were stratified according to disease severity and randomized to receive either TPN or TEN for 7 days and then re-evaluated. Clinical outcome parameters (incidence of SIRS, sepsis, multiple organ failure, operative intervention and mortality) were measured at follow-up.

Clinical outcome, such as SIRS, sepsis, organ failure and length of time in the intensive treatment unit, were globally improved in the patients fed enterally. The acute-phase response and disease severity scores were significantly improved following enteral nutrition CRP (156 (117–222) to 84 (50–141), $P<0\cdot005$) and APACHE II scores (8 (6–10) to 6 (4–8), $P<0\cdot0001$) without change in the CT scores. In patients fed parenterally these parameters did not change but there was an increase in EndoCAb antibody levels (74(19) per cent) and a fall in TAC (30(9) per cent). Patients fed enterally showed no change in the level of EndoCAb antibodies and an increase in TAC (20(14) per cent). These data indicate that TEN moderates the acute-phase response and improves disease severity and clinical outcome despite unchanged pancreatic injury on CT. In addition, these data provide evidence of reduced systemic exposure to endotoxin and reduced oxidant stress. Thus gut mucosal feeding modulates the inflammatory and sepsis response in acute pancreatitis and is clinically beneficial.

Intra-abdominal and systemic activity of soluble adhesion molecules in human intra-abdominal infection

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Endothelial cell- and neutrophil-derived adhesion molecules can induce inflammatory processes. The authors studied immunomechanistic aspects of intra-abdominal infection (IAI) with regard to adhesion molecule activation compared with cytokine release patterns. To date, only adhesion molecule release into the circulation has been studied. This study analysed local activity of adhesion molecules in exudate from human peritonitis. In 22 patients with severe IAI, levels of selectin E, L and P as well as interleukin (IL) 6 and IL-8 were measured in peritonitis exudate and serum, drawn during the operation.

Levels of IL-6 and IL-8 were raised in serum (6·0(9·1) ng/ml and 1·6(3·2) ng/ml, $P<0{\cdot}001$) and even more so in the peritoneal cavity, at the focus of inflammation (53·5(63·6) ng/ml and 83·3(66·2) ng/ml, $P<0{\cdot}001$). In contrast, endothelial cell-derived P- and E-selectin serum levels were only moderately raised (316(195) ng/ml and 181(63) ng/ml respectively), and also, but even less detectable, in peritonitis exudate (164(98) ng/ml and 76(49) ng/ml respectively, $P<0{\cdot}05$) Polymorphonuclear neutrophil (PMN)-derived L-selectin was not significantly raised either systemically or in peritonitis exudate (0·89(0·52) and 1·48(1·38) μg/ml respectively). These data demonstrate that in human IAI endothelial cell-derived adhesion molecules are activated in the circulation and also occur intraperitoneally Even in purulent exudates, however, PMNs released only low amounts of adhesion molecule compared with cytokine production or release of lysosomal enzymes. Apparently in intra-abdominal local defence the activation of adhesion molecules is of small importance compared with other PMN activities.

Monitoring of the peritoneal inflammatory response after elective abdominal surgery

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The inflammatory reaction of peritoneum after elective abdominal surgery compared with systemic acute-phase reaction is not well known. The authors evaluated this reaction by measurement of inflammatory mediators and differentiation of leucocytes in peritoneal exudate and peripheral blood. In 31 patients undergoing major abdominal surgery (gastric and pancreatic resection), three drain tubes were inserted intraoperatively in standardized positions. Peritoneal exudate tubes and blood were collected and examined daily during the first 5 postoperative days. Endotoxin was measured with the LAL test, interleukin (IL) 6 with enzyme-linked immunosorbent assay techniques, C-reactive protein (CRP), apolipoprotein A$_1$ and transferrin, using nephelometry, and leucocytes were counted and differentiated in both exudate and blood.

Endotoxin and IL-6 values in exudate were 10–200-fold higher than their values in blood during measurement (exudate median endotoxin 0·38–0·76 EU/ml; IL-6 21 140–54 920 pg/ml; blood· endotoxin 0–0·07 EU/ml, IL-6 17–149 pg/ml). The time courses of mediators and leucocytes in exudate were· endotoxin constantly but slightly increased; IL-6 decreased until the fourth day, and then increased; CRP increased until the fourth day and then decreased; apolipoprotein A$_1$ and transferrin did not change; the leucocyte count decreased (median (range) cells/mm^3: day 1, 2887 (110–16 940); day 5, 1100 (0–31 295)). The proportion of polymorphonuclear leucocytes (PMN) decreased in exudate, while that of lymphocytes increased (PMN· day 1, 90–96 per cent, day 5, 24–67 per cent, lymphocytes: day 1, 4–9 per cent; day 5, 33–74 per cent). The leucocyte count in blood declined (median (range) g/l: day 1, 10 300 (4500–24 000); day 5, 6800 (3500–15 800)) In contrast, the left shift of blood film remained constant. Excessive damage to cells by intracellular Gram-positive cocci was observed in exudate from 11 patients.

A severe inflammatory reaction of the peritoneum, measured by intraperitoneal mediators and cell differentiation, takes place many days after elective abdominal surgery. This reaction is unrelated to the short systemic acute-phase reaction. The influence of this inflammatory reaction of peritoneum on the postoperative clinical course is not known and needs further study.

Yeast colonization and infection in burned patients

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A cohort of 2649 consecutively admitted burned patients was followed from admission to discharge for yeast colonization and infection using a consistent microbial surveillance culture programme and prospectively defined site-specific definitions of infection. Surveillance sputum, wound, stool and urine cultures were taken three times per week. Blood cultures, wound biopsies and cultures from other sites were performed as clinically indicated. Colonization was defined as isolation of a yeast species from non-infected sites.

Yeast species were isolated from 775 patients (29·3 per cent). Within 4071 isolates, seven species were identified. The most common sites of isolation were stool (28·2 per cent) and urine (24·9 per cent) *Candida albicans* was the most common colonizer (63·2 per cent) A total of 175 yeast infections occurred in 118 patients. Yeast infections were identified at a mean of 45 days post-injury and represented 12 per cent of all infections. The urinary tract was the most common site (57·1 per cent) and *C albicans* was the most frequent yeast pathogen (58·9 per cent). Urinary tract infections were more common in women ($P<0{\cdot}01$). Yeast infection was associated with more severe injury. Mean burn size and age-related mortality predictor was 55·4 per cent for yeast-infected patients compared with 11·5 per cent of patients without yeast infection Patients with yeast infection did not have an increased mortality above that predicted based on injury severity

Yeast colonization (even at multiple sites) is not a reliable predictor of yeast infections (only 15·2 per cent of colonized patients became infected). The high incidence of urinary tract infection among female patients with burn injury suggests the need to improve local care and perhaps the use of topical antifungal agents prophylactically.

Use of shock index as a prognostic factor in patients in the intensive care unit with systemic inflammatory response syndrome

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Shock index has been used as a marker in post-traumatic patients and in experimental models in order to detect hypovolaemia. Shock index is defined as pulse rate per systolic blood pressure. Systemic inflammatory response syndrome (SIRS) is defined by several physiological parameters (pulse rate, respiration rate or PaCO$_2$ level, temperature and leucocyte count) and represents an activated state of the immune system with features of hypovolaemia and tissue dysoxia Patients with SIRS are thought to be at risk of developing complications, such as sepsis. Hypovolaemia can be used to identify patient groups with a higher mortality rate and a higher rate of sepsis

A total of 166 patients was evaluated Of these, 94 stayed more than 24 h on the intensive care unit (ICU) and were included in the study Shock index was calculated at time 0 and the lowest value during the first 24 h after admission. As an indication of tissue dysoxia, lactate was measured routinely at admission. Endpoints. multiorgan failure (Goris) and early mortality on ICU.

Group	10-day survival	Shock index (0 h)	*P*	Shock index (24 h)	*P*
Total group (*n* = 94)	Survivors (*n* = 75)	0·94	n.s.	0·75	0·0025
	Non-survivors (*n* = 17)	1·04		1·20	
Patients after operation	Survivors (*n* = 29)	0·72	n.s.	0·75	0·045
	Non-survivors (*n* = 6)	0·73		1·08	
Non-operative patients	Survivors (*n* = 46)	0·74	0·022	0·72	0·0001
	Non-survivors (*n* = 11)	1·28		1·22	

n.s., Not significant

Patients with a shock index greater than or equal to 1·2 had a higher organ failure score (4·7 *versus* 2·9), $P=0{\cdot}012$. Lactate in patients after operation with a shock index greater than or equal to 1·2 = 9·7 or shock index less than 1·2 = 1·7 ($P=0{\cdot}002$) indicating the presence of tissue dysoxia. Shock index can be used as a prognostic marker in patients with SIRS on the ICU for short-term survival and organ failure. Shock index measured during 24 h after admission is more important than at admission; it appears to be of more predictive value in patients who have not undergone operation.

Immune and metabolic effects of perioperative immunonutrition

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Major abdominal operations are associated with alterations of the immune and inflammatory responses and gut function. The trial evaluated the perioperative administration of immunonutrients in patients undergoing surgery for cancer of the stomach or colorectum. Seven days before surgery the patients drank 1 litre per day of either a standard (S) enteral formula ($n=20$) or the same formula enriched (E) with arginine, RNA and n-3 fatty acids ($n=20$) After operation jejunal infusion was started within 6 h and progressively increased to the full regimen (25 kcal/kg) on day 3 after operation Enteral feeding was continued until day 7. Immune response was evaluated by phagocytosis of zymosan by polymorphonuclear neutrophil (PMN) cells (as percentage of total PMNs), CD4/CD8 ratio and composite score of delayed hypersensitivity response (DHR) to skin tests (the higher the score, the lower the DHR). Intestinal microperfusion (laser Doppler) during operation and mucosal oxygen metabolism (tonometry, pH_i) after surgery were used as indicators of gut function. The inflammatory response was evaluated by plasma levels of C-reactive protein (CRP) The two groups were comparable for all the baseline parameters studied. One day after surgery the group receiving the enriched diet showed significantly higher ($P<0{\cdot}05$) PMN phagocytosis ability (47(5) *versus* 37(6) per cent), CD4/CD8 ratio (2·7(1·3) *versus* 1·7(1·4)) and pH_i (7·39(0·2) *versus* 7·33(0·1)) than the control group, while lower values of DHR composite score (0·63(0·18) *versus* 0·89(0·21)) and CRP (80(34) *versus* 121(64) g/l) were found in the E group than in the S group. Ileal perfusion was 180(46) (perfusion units) at the beginning of surgery in the E group *versus* 146(59) in the S group ($P<0{\cdot}05$) Colonic perfusion followed a similar trend.

The perioperative administration of an enriched enteral formula improves intestinal perfusion and oxygenation and positively modulates the immune and inflammatory responses

Effect of thymocartin on systemic inflammatory response syndrome: importance of host response

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The authors have shown that thymocartin (TP4) (thymic peptide Arg-Lys-Asp-Val) can downregulate, but not abolish, the lipopolysaccharide (LPS)-induced tumour necrosis factor (TNF) α secretion in whole blood cultures. This downregulatory effect of TP4 on TNF-α production may modulate the systemic inflammatory response syndrome (SIRS) following trauma.

Sixteen patients with SIRS, characterized by markedly raised C-reactive protein (CRP), severe lymphopenia, fever and unstable circulation, were treated with five subcutaneous injections of TP4 during a period of 10 days. In the 2 weeks following the last administration of TP4 eight of 11 patients with high serum TNF-α levels recovered TNF-α and CRP levels and lymphocyte counts normalized, and circulation stabilized. Three of five patients with low TNF-α levels died in the 2 weeks after the last administration of TP4 Serum level of TNF-α was 6109(3740) U/ml in the group with high TNF-α and 344(297) U/ml in the group with low TNF-α before TP4 treatment. Seventeen patients with SIRS were not treated with TP4 and served as controls. Thirteen patients with low TNF-α and three patients with high TNF-α levels died; only one survived.

These findings suggest strongly the beneficial effect of thymic peptide on patients with SIRS and high TNF-α release. TNF-α production can be hazardous in excess, but dangerous if decreased.

Polymorphonuclear neutrophil dysfunction in patients with cirrhosis

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Patients with cirrhosis have an increased susceptibility to develop bacterial infections, among them spontaneous bacterial peritonitis (BP). Several polymorphonuclear neutrophil (PMN) dysfunctions have been reported, mainly focused on opsonic phagocytic capacity. This study assessed additional functions related to *in vivo* PMN migration and phagocytic activity in patients with cirrhosis. Twenty-two of these patients and six healthy volunteers were enrolled in this study. Several skin blister windows were performed and filled with (1) streptokinase in autologous serum; (2) killed fluorescein-labelled *Escherichia coli* (KFLE) in autologous serum; (3) KFLE in ascitic fluid. Some 12 h later, exudated PMNs were determined by flow cytometry. Mean channel number was transformed into molecular equivalents of soluble fluorescein (MESF) and the number of receptors per cell determined with fluorescent beads.

CD11b/CR3 in circulating PMNs was significantly increased in patients with cirrhosis compared with the healthy volunteers (60 878(20 698) *versus* 30 113(1681) receptors per cell, $P<0{\cdot}005$). The number of exudated PMNs was decreased in cirrhotic patients compared with healthy volunteers (1 135 371(62 412) *versus* 2 234 405(71 191), $P<0{\cdot}05$), as well as the phagocytic capacity in serum (MESF 242 529 (21 156) *versus* 339 469(17 017), $P<0{\cdot}005$). In subgroup analysis, cirrhotic patients who suffered spontaneous BP showed an impaired phagocytic activity that was decreased even further in ascitic fluid (109 855 (17 602) *versus* 171 250(31 940), $P<0{\cdot}005$)

PMNs of cirrhotic patients show a decreased capacity to migrate to foci with both Gram-positive and Gram-negative antigens. PMN delivery and phagocytic capacity are even more impaired in the peritoneal fluid microenvironment.

Taurine sequestration after operation modulates neutrophil reactive oxygen species generation

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Taurine is a β-amino acid and has been shown to be protective against endothelial cell injury, possibly by modulation of superoxide free radical generation. This study evaluated the effect of surgical injury on neutrophil superoxide respiratory burst activity (RBA) and aimed to clarify the role of plasma taurine in modulation of neutrophil RBA.

Patients undergoing elective abdominal surgery had whole venous blood taken immediately before operation (T0), T6 and at T24 h. RBA was analysed using flow cytometry. Neutrophils were isolated with dextran sedimentation and Ficol gradient centrifugation and suspended at a concentration of 5×10^6 per ml. Intracellular taurine was measured by high performance liquid chromatography following conjugation of taurine with sodium hypochloride to form its chlorinated derivative.

	Time 0 h	Time 6 h	Time > 24 h
RBA	164(40)	92(17)*	93(44)*
PMN taurine	0·74(0·33)	1·38(0·33)*	1·60(0·11)*
Plasma taurine	82·1(41·9)	–	49·5(19·3)*

Mean(s.d.) channel fluorescence. PMN, polymorphonuclear neutrophil. Taurine (μmol). *$P<0\cdot05$

Neutrophil RBA was significantly downregulated from 6 h after operation ($P<0\cdot05$). Neutrophil intracellular taurine was significantly increased from preoperative values (0·74(0·33) μmol, $P=0\cdot007$) and at 24 h after operation (1·60(0·11) μmol, $P=0\cdot001$).

The authors have demonstrated that postoperative neutrophils sequester plasma taurine in order to modulate reactive oxygen species generation, confirming the importance of taurine in maintaining neutrophil homoeostatic function. These preliminary results demonstrate a potential role for perioperative taurine supplementation to attenuate surgically induced endothelial injury.

Effects of nitric oxide donation on liver blood flow in a porcine model of continuous portal endotoxaemia

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Nitric oxide synthase inhibitors are detrimental to splanchnic perfusion. L-arginine provides improved liver perfusion during ischaemia–reperfusion and endotoxaemia. The authors determined whether early administration of the nitric oxide (NO) donor sodium nitroprusside (SNP) as opposed to NO blockade during endotoxaemia would improve liver perfusion. Five pigs were anaesthetized and tracheostomized. Animals received a continuous infusion of 10 ml/h 0·9 per cent NaCl. Catheters were inserted into the right hepatic vein, pulmonary artery and femoral artery. After laparotomy ultrasonic flowprobes were attached to the portal vein and the hepatic artery and two mesenteric veins were cannulated. After closure of the abdomen animals were equilibrated for 1 h. Thereafter, study animals received a continuous infusion of 1·7 μg/kg/min *Escherichia coli* endotoxin (ET) and 6 μg/kg/min SNP to the portal vein and were studied for 4 h. Seven animals from an earlier part of the same experiment, receiving only ET, served as controls. Results were compared by analysis of variance for repeated measures.

Both ET and ET/SNP led to a significant continuous decrease of mean arterial pressure by 20 per cent (ET) and 40 per cent (ET/SPN) at 3 h ($P<0\cdot01$). While ET caused a significant decrease of hepatic artery flow (QHA) by 52 per cent at 3 h ($P<0\cdot02$), simultaneous administration of SNP led to an increase of QHA at 1 h, a maintenance of QHA at 82 per cent at 3 h, and a constant increase in hepatic artery conductance (HAC). Hepatic artery resistance increased in controls to 142 per cent at 3 h ($P<0\cdot03$) and at the same time decreased to 46 per cent in SNP animals. Simultaneously, portal venous flow (QPV) decreased significantly by 30 per cent (ET) and 45 per cent (ET/SNP), leading to an overall decrease in total hepatic blood flow in both groups ($P<0\cdot05$). Portacaval resistance increased in both groups up to 160 per cent (ET) and 190 per cent (ET/SNP) at 3 h though not statistically significantly. Early administration of SNP during endotoxaemia improves arterial blood supply to the liver, but not portal venous flow. The increase in QHA and HAC along with reduced QPV may be due either to direct action of SNP or to a SPN-induced restitution of the hepatic artery buffer response which is normally lost during endotoxaemia.

Peritoneal responses to peroperative lavage – *in vitro* and *in vivo* observations

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Peroperative lavage has become a standard procedure to clean a contaminated or potentially contaminated abdominal cavity. However, irritation of the peritoneal surface with lavage solutions may interfere with peritoneal defence mechanisms. Peritoneal mesothelial cells (MCs) contribute directly to proinflammatory events and local fibrinolytic and procoagulant activity. Viability and functional properties of human MCs after exposure to different lavage solutions were affected *in vitro*. The authors evaluated the effect of peroperative lavage on postoperative peritoneal responses *in vivo*. Drain fluid of 15 patients undergoing elective abdominal surgery with (NaCl 0·9 per cent and distilled water) or without lavage were collected (6 and 24 h). They determined intraperitoneal cell injury (lactate dehydrogenase release) and activation (synthesis of interleukin (IL) 6 and IL-8, tissue plasminogen activator (tPA), plasminogen activator inhibitor (PAI) 1 and tissue factor).

Lavage caused raised LDH release due to cell injury. Cytokine concentrations were significantly depressed in the 6 h drain fluid of lavaged cavities. For distilled water the proinflammatory cytokine concentration after 24 h was enhanced. The exposure of the peritoneal cavity to lavage solutions induced PAI-1 antigen synthesis more. Aqua dest induced a significant increase of tissue factor antigen after 24 h. Peritoneal lavage solutions are cytotoxic. Irrigation depresses proinflammatory cytokine concentrations in the early period after operation, and only distilled water increases IL-8 concentration after 24 h. The increase of an important inhibitor of the fibrinolytic cascade (PAI-1) by lavage solutions (distilled water more than NaCl) may be of clinical relevance. Modulation of functional properties of MCs by an intraperitoneal instilled non-cytotoxic solution is a promising target in the treatment of peritonitis.

Does peritonitis influence the energy content of the colon wall? Results from an animal model with and without antibiotic therapy

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In former studies an abscess-forming peritonitis was induced in rats after laparotomy and innoculation of a *Bacteroides fragilis* suspension. After 3 and 7 days a severe polymicrobial intra-abdominal infection resulted through translocation of gut bacteria into the abdominal cavity but the mechanism of translocation was unknown. In this experiment the authors studied the content of adenosine triphosphate (ATP) in the colon wall in the same peritonitis model with and without therapy. In 53 untreated animals, after innoculation of *B. fragilis* (10^9 colony-forming units per ml), a chronic abscess-forming peritonitis was induced. Twenty-four hours after, innoculation of bacteria, antibiotic treatment in another 21 animals was started with tazobactam–piperacillin (twice per day 45 mg intramuscularly). Treated and untreated groups were divided into three subgroups, which were observed for 3, 7 and 14 days respectively. ATP was measured by luminometry (562 nm).

Translocation occurred in two of 53 untreated rats (*B. fragilis* and streptococci). Intra-abdominal abscesses were found on days 3, 7 and 14 in two, 13 and 12 animals of the untreated peritonitis group respectively, and in 0, one and one animals of the antibiotic group. In the untreated group the ATP levels were 542, 570 and 655, and in the antibiotic group 695, 821 and 797 nmol/g. The energy content (ATP) of the colon wall in untreated peritonitis was markedly lower in contrast to the group treated with antibiotic. Intra-abdominal abscesses possibly caused decreased ATP. However, a lower energy content in the colon wall could correlate directly with translocation in peritonitis.

Local inflammatory peritoneal response to operative trauma: studies on cell activity, cytokine expression and adhesion molecules

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Peritoneal trauma caused by intra-abdominal operation is reflected by an ill defined influence on homoeostasis. The authors investigated the local peritoneal response to different surgical procedures.

In ten patients with laparoscopic (cholecystectomy (four), fundoplication (one)) or conventional open surgery (low anterior resection (one), small bowel resection (one), gastrectomy (one), gastroenterostomy (one), laparotomy only (one)), peritoneal specimens were taken from the incision or resection margins at the beginning and end of intervention Mean (range) length of operating time was 105 (40–150) min for the laparoscopic group and 136 (30–300) min for the open group. Monocyte–macrophage activity was assessed immunohistochemically using the antibody clone HAM 56 for local macrophages and antibodies against macrophage–inhibiting factor (MIF)-related proteins 8 and 14 (MRP 8 and 14). Antibacterial protein (defensin 3) reflected the activation of granulocytes. Cellular expression of interleukin (IL) 1, IL-6 and intercellular adhesion molecule (ICAM) 1 was also measured. All examinations were performed in paraffin sections using the avitin–biotin complex technique.

ICAM-1 was expressed in the interstitium of all patients with no activation of local macrophages (HAM 56) Expression of MRP 8 and 14 as well as defensin 3 showed a diffuse positivity in all parts of the peritoneum, especially in patients with extended operations. IL-1 and IL-6 were expressed by mesothelial cells and submesothelial tissue dependent on the extent of the operation. In long procedures IL-1 reactivity was reduced.

From these results it is concluded that both the duration and the kind of procedure determine the expression of cellular activity. Regarding the different procedures minimally invasive surgery does not consistently mean minimal peritoneal trauma. The immunohistochemical evaluation of the local cellular response may provide objective criteria for the grading of operative trauma.

Effect of granulocyte–macrophage colony-stimulating factor on bacterial translocation after experimental obstructive jaundice

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Bacterial translocation (BT) is the movement of viable indigenous micro-organisms across the intestinal barrier. Obstructive jaundice is known to play an important role along with many other aetiological factors. Granulocyte–macrophage colony-stimulating factor (GM-CSF) is a 22-kD glycoprotein hormone that is produced by activated T lymphocytes and induces immune function. In this study the authors investigated the therapeutic effect of GM-CSF treatment of obstructive jaundice on bacterial translocation. Thirty male Wistar rats were divided randomly into three groups Group 1 (ten) received a sham operation (controls), group 2 (ten) and group 3 (ten) underwent common bile duct ligation and division. Animals in group 3 were then treated with 200 ng GM-CSF subcutaneously from days 5 to 9 after operation. All animals were killed 10 days after the operation by cervical dislocation and cardiac puncture. Besides biochemical and histopathological examination, the mesenteric lymph nodes were cultured under aerobic and anaerobic conditions

While BT could not be detected in groups 1 and 3, *Escherichia coli* and *Salmonella typhimurium* were found in four and two rats respectively in group 2 Anaerobic bacteria were not detected. Compared with zero incidence in groups 1 and 3, rats that had not been treated with GM-CSF had a 60 per cent incidence of BT. Statistically, this was found to be significant ($P<0\cdot001$). As a result of this study, failure in immune function due to obstructive jaundice, which is one of the causal factors of BT, was examined and GM-CSF treatment was observed to be of benefit.

Alteration of antimicrobial granulocyte functions by recombinant human granulocyte colony-stimulating factor and antibiotics: a source of heterogeneity in clinical cytokine trials?

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Almost all multicentre trials in sepsis have failed and several models have been developed to explain this patient heterogeneity, different phases of the disease process and trial errors. Differences in patient management have not been systematically studied. The interaction of rhG-CSF (recombinant human granulocyte colony-stimulating factor) with various antibiotic regimens has been analysed in a clinically adapted rat model. In randomized studies with 600 male Wistar rats with abdominal contamination and infection (ACI) the prophylactic use of rhG-CSF was assessed in combination with co-amoxiclav, cefuroxime-metronidazole, ceftriaxone, cefotaxime, ofloxacin, imipenem and amikacin. In each trial four groups were compared: saline, antibiotic (AB) alone *versus* AB and rhG-CSF ($3\times20\,\mu$g/kg or $1\times50\,\mu$g/kg). The endpoint was the 5-day mortality rate. The white blood count, polymorphonuclear neutrophil ratio, migratory activity and production of superoxide anions were also analysed.

All antibiotics reduced the mortality rate, but a further significant ($P<0\cdot05$) reduction with rhG-CSF was obtained only by the combination with co-amoxiclav and cefuroxime–metronidazole. In the experiments with rhG-CSF ($3\times$) the animals showed a lower mortality rate than with rhG-CSF ($1\times$) in combination with cefuroxime, imipenem, amikacin and ofloxacin. Antimicrobial functions of the granulocytes were increased by AB alone and in an additive manner with rhG-CSF. Antibiotics and rhG-CSF alter mortality rates and change antimicrobial functions of granulocytes in different ways. Heterogeneity in the effects of rhG-CSF in multicentre studies can be expected on the basis of these experiments.

Inhibition of angiotensin II ameliorates trauma- and sepsis-induced gut mucosal injury and bacterial translocation

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As the angiotensin II inhibitor DuP753 has been reported to ameliorate burn- and sepsis-induced gut ischaemia, the authors investigated whether DuP753 treatment can attenuate mucosal injury and bacterial translocation in a burn–endotoxaemia chronic porcine model. Twenty-one pigs (20–25 kg) were anaesthetized and 14 received 40 per cent total body surface area third-degree burn. DuP753 was administered intravenously in a dose of $1\,\mu$g/kg to seven pigs immediately after burn. Eighteen hours after burn, $100\,\mu$g/kg *Escherichia coli* lipopolysaccharide (LPS) was administered intravenously. Plasma conjugated dienes (PCDs), index for lipid peroxidation following ischaemia–reperfusion injury, were measured every 6 h. Intestinal permeability was also assessed every 6 h, by measuring the lactulose/mannitol (L/M) excretion ratio. At the end of the study (42 h), tissue samples were harvested for bacteriological cultures.

PCD levels were significantly raised 8 h after burn (182 per cent increase *versus* sham, $P<0\cdot01$). LPS caused a higher and prolonged increase in PCD levels (201 per cent of baseline). Treatment with DuP753 significantly reduced PCD levels after burn and after LPS ($P<0{\cdot}01$). Intestinal permeability, as assessed by L/M ratio, showed a 6- and 12-fold increase after thermal injury and LPS respectively ($P<0{\cdot}05$). In contrast, L/M ratio had only a 2-fold increase in animals treated with DuP753 ($P<0{\cdot}01$) Bacterial translocation was significantly increased after burn and endotoxin (six of seven *versus* one of seven sham, $P<0{\cdot}05$) Incidence of bacterial translocation in the animals treated with DuP753 was similar to that of the sham group (two of seven). Angiotensin II appears to play a pivotal role in burn- and endotoxin-induced intestinal ischaemia–reperfusion injury, with subsequent increased permeability and bacterial translocation. Administration of the angiotensin II receptor antagonist, DuP753, after burn significantly reduces the extent of these events.

Randomized comparison of cefoperazone–sulbactam and imipenem–cilastatin in the treatment of intra-abdominal infections

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Antibiotics have a secondary but non-negligible role in the treatment of secondary bacterial peritonitis and intra-abdominal abscesses caused by aerobes and anaerobes. Monotherapeutic agents are safe and effective in the treatment of intra-abdominal infections The present study was carried out on patients who were surgically treated for intra-abdominal infections. Fifty patients were studied and randomized into two groups. Group 1 received intravenous imipenem–cilastatin 1 g per 24 h and group 2 received intravenous cefoperazone–sulbactam 2 g per 24 h The mean age of patients was 46·1 and 50·8 years for groups 1 and 2 respectively. The patients were evaluated for Acute Physiology And Chronic Health Evaluation (APACHE) II scores at admission and after treatment. Cultures were taken at operation.

Mean APACHE II score at admission was 14·3 and 12·7 for groups 1 and 2 respectively. Secondary peritonitis due to delayed peptic ulcer and appendiceal perforations was responsible in most of the patients in both of the groups. Mean length of stay in the intensive care unit was 6 days for group 1 and 8 days for group 2. In group 1, 17 patients had recovery and six patients had resistance to antibiotic treatment. In group 2, 14 patients recovered and eight patients had resistance to antibiotics *Staphylococcus aureus* and *Escherichia coli* were the most frequently isolated micro-organisms. The mean APACHE II scores after treatment were 9·6 and 8·5 for groups 1 and 2 respectively. Two patients in group 1 and three patients in group 2 had postoperative intra-abdominal abscess and all patients underwent percutaneous drainage with computed tomography. Five patients in each group had wound infections Two patients in group 1 died (myocardial infarction and septic shock) in the early postoperative period For patients with high APACHE scores, imipenem–cilastatin and cefoperazone–sulbactam can be used as effective agents in the treatment of intra-abdominal infections. The authors could not demonstrate any superiority of one combination over the other.

Induction of endotoxin tolerance by atoxic endotoxin – a new prophylactic concept to the septic syndrome

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Repeated small doses of endotoxin (ET) induce resistance to subsequent larger doses of ET. This preconditioning, termed ET tolerance, is a well controlled active response which can prevent excessive inflammation

The distantly related Gram-negative bacteria, like the sulphur-containing or sulphur-free purple bacteria, appear to have low endotoxicity or to be completely non-toxic but maintain many beneficial immunomodulatory activities.

This experiment was designed to test the response to the non-toxic ET of *Rhodopseudomonas sphaeroides* to protect animals after 5 days of immunization against a continuous ET challenge dose of 250 ng per kg body-weight per hour over a 12-h observation period.

Time after ET	Group	0	2	4	6	8	10	12
MAP								
(mmHg)	C	88	73	63	61	56	–	–
	T	79	70	73	68	71	80	78
HR								
(per min)	C	72	101	136	172	151	–	–
	T	69	75	82	85	104	103	96
CO								
(l/min)	C	3·3	3·0	2·8	2·3	1·9	–	–
	T	3·2	3·6	2·7	2·3	2·4	2·5	2·7
S_{VO_2}								
(mmHg)	C	47·2	39·4	42·1	43·0	48·3	–	–
	T	42·1	46·1	39·9	33·2	38·0	37·6	39·5

MAP, mean arterial pressure; HR, heart rate; CO, carbon monoxide; S_{VO_2}, venous saturation of oxygen

Survival time was enhanced significantly ($P<0{\cdot}01$) in the tolerant group (T) in comparison to the controls (C) from 490 to 670 min. The encouraging results of this study emphasize the potential role of atoxic ET as a therapeutic agent. As a new prophylactic approach ET tolerance may prevent septic complications The tolerance state, however, is never complete and can be overcome by raising the ET challenge or adding other negative stimuli like a second or subsequent hit

Promotion of healing in infected wounds by 'vacuum sealing'

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This study evaluated the benefit of 'vacuum sealing' (VS) in healing infected non-traumatic wounds. The basic idea of VS is continuous vacuum drainage from the wound surface. The tissue defect was filled in with open porous polyvinylalcohol foam in which two perforated drainage tubes were inserted Their distal drain ends were drawn from the wound through the skin. The wound surface was covered with a semipermeable polyurethane drape. The drainage tubes were connected to the vacuum bottles creating a vacuum in the entire wound. Twenty-nine patients had a VS procedure. All of them had large (5 cm in length or more) infected wounds of the soft tissues. The mean time of sealing was 7·3 days. In 25 patients clinical improvement was achieved. The histological findings after VS demonstrated less necrosis, fewer inflammatory cells and more functional vessels. The favourable result may be due to the prompt evacuation of fluids, containing bacteria and their toxic byproducts, and to the high pressure at the interface between the foam and the wound which stimulated granulation tissue growth.

Incidence of systemic inflammatory response syndrome and organ failure on a mixed intensive care unit – the definitions evaluated

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Systemic inflammatory response syndrome (SIRS) is defined by several physiological parameters (pulse rate, respiration rate, temperature, leucocyte count) and is seen as a precursor state for the development of sepsis and organ failure SIRS criteria

	Excluding postoperative trauma				Including postoperative trauma patients				
	0 h		24 h		0 h		24 h		
Time	SIRS $n=45$	No SIRS $n=49$	SIRS $n=37$	No SIRS $n=57$	SIRS $n=66$	No SIRS $n=28$	SIRS $n=55$	No SIRS $n=39$	P
Day 10	82·5%	60·0%	77·8%	88·9%	71·4%	81·8%	76·4%	94·4%	0·047
Day 30	70·0%	40·0%	66·7%	66·7%	42·0%	62·7%	52·7%	83·3%	0·011
MOF	3·9	3·4	3·9	3·6	3·9	3·4	4·3	2·6	0·009

have been formulated by expert opinion and are not based on data. Changes after surgery or trauma may be the result of physiological changes. Furthermore, it is not clear to what extent the different definitions of SIRS have prognostic implications A prospective study has been performed to study the predictive value of SIRS in patients in the intensive care unit (ICU). Only patients with an ICU admission of over 24 h were included. SIRS criteria were obtained at admission and during the first 24 h after admission. Endpoints were occurrence of multiple organ failure (MOF or Goris score) and mortality at days 10 and 30. In total, 94 patients were studied.

Excluding surgical patients from the group with SIRS reduces the apparent incidence of the syndrome. However, including these patients improves the prognostic significance of the SIRS criteria Sustained SIRS (still present at 24 h) is more important than SIRS at admission as a prognostic marker for the development of organ failure and mortality

Changing microbiological pattern of inflammatory diseases of the pancreas after operation and reoperation

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This prospective study evaluated the bacteriological status of patients with inflammatory pancreatic disease which caused intra-abdominal fluid collection during the course of surgical treatment

A total of 86 consecutive patients underwent operation between January 1994 and December 1995. The 14 patients who were not tested bacteriologically either at the first operation or at reoperation were excluded. At first operation 22 patients (31 per cent) were infected. Mainly Enterobacteriaceae were cultured. The number of pathogens per positive patient was 1·6. Further operations were needed in 28 patients. Intra-abdominal pathogens could be cultured in 23 patients (82 per cent) at reoperation. The characteristic pathogens were the Enterobacteriaceae, *Pseudomonas aeruginosa, Acinetobacter calcoaceticus* and enterococci. The number of pathogens per positive patient was 2·1. At third and fourth reoperation all patients ($n=17$ and $n=$seven patients) had a positive culture with an increased predominance of enterococci, Enterobacteriacae and *P. aeruginosa*. The number of pathogens per patient did not increase The protracted stay in the intensive care unit was associated with colonization of patients, and recurring surgical interventions resulted in selection of the resistant pathogens.

Tube thoracostomy for haemopneumothorax and the need for antibiotic prophylaxis

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Haemopneumothorax after penetrating chest trauma requires tube thoracostomy Infection may result from intitial pleuropulmonary contamination and the presence of a drain as foreign body for a few days. Antibiotic prophylaxis has not been shown conclusively to be beneficial and may have some drawbacks. The authors undertook a prospective randomized controlled study to evaluate antibiotic prophylaxis in a trauma centre dealing with large numbers of chest injuries. During a 1-year period (August 1995–September 1996) more than 500 patients were admitted with penetrating chest trauma requiring intercostal drainage. Only patients fulfilling specific entrance criteria were included in the study After 300 had been recruited the trial was discontinued. There were 242 men and 58 women with a median age of 26 years. All patients received a single dose of bicillin on admission and, if eligible, were randomized to receive either no further antibiotics (control group) or amoxycillin–clavulanic acid (Augmentin group). Augmentin was given as a dose of 750 mg at insertion of chest drain and 375 mg three times per day orally and thereafter until the first day after extubation. Clinical, haematological, radiological and microbiological criteria were used for the definition of infection

A total of 264 patients were analysed, 137 of whom received Augmentin and 127 served as controls. Infection diagnosed on one criterion occurred in 66·4 per cent (91 of 137) in the Augmentin group and 78·7 per cent (100 of 127) in the control group (P not significant) On the basis of two criteria, for example clinical plus radiological, the incidence of infection was 13·1 per cent (18 of 137) for Augmentin and 15·7 per cent (20 of 127) for the control group. The rate of infective complications was higher for gunshot wounds than for stab wounds (21.8 *versus* 13·3 per cent, $P<0·05$). Factors such as delay and duration of chest drain influenced the outcome, and infection prolonged the hospital stay. *Staphylococcus aureus, Klebsiella pneumoniae* and *Acinetobacter* were among the commonest organisms isolated. Although no statistical difference was noted, these findings suggest that patients requiring tube thoracostomy for trauma should receive the benefit of systemic prophylactic antibiotic therapy.

Efficacy of thymopentin (TP-5) in the restoration of delayed hypersensitivity responses in jaundiced and anergic rats

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This study determined the value of thymopentin in jaundiced and anergic rats to return the state of immunocompetence. Male Wistar rats weighing 250–300 g were injected with haemocyanin (KLH) for testing delayed-type hypersensitivity (DTH) response. All rats with a positive response were included in the study and the authors evaluated the T cell subpopulations CD3, CD4 and CD8. The animals underwent laparotomy and the common bile duct was ligated and divided. Rats that had become jaundiced and anergic 1 week after the operation were divided into two groups: control (six) and treatment TP-5 (18) at a dose of 0·02 mg/kg intramuscularly per day during 7 days.

Of the 37 rats that responded to KLH, 23 survived the operation, and division of the bile duct was accompanied by anergy in 100 per cent during the first week. Of the 23 jaundiced (total bilirubin 12·8 mg/dl) and anergic rats that were submitted to treatment with TP-5, 18 survived and all recovered immunocompetence at the end of the week of treatment. The treatment with TP-5 for 1 week improves the level of CD3 in jaundiced and anergic rats (baseline 70·7 per cent; first week after operation 60·3 per cent; second week after operation 62·8 per cent (control group); second week after operation with TP-5 72·1 per cent (control *versus* TP-5, $P<0{\cdot}05$)). Obstructive jaundice in rats is accompanied by anergy and the administration of thymopentin (TP-5) leads to a return of cellular immunocompetence.

Antibiotic prophylaxis in acute necrotizing pancreatitis

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In acute necrotizing pancreatitis the clinical course is mainly determined by septic complications caused by bacterial infection of pancreatic necrosis. The effect of antibiotic prophylaxis in necrotizing pancreatitis was evaluated in this study.

Twenty-six patients with sterile necrosis were randomly assigned to receive either intravenous ofloxacin 2 × 200 mg and intravenous metronidazole 2 × 500 mg, or to serve as controls (no antibiotics).

The median amount of necrosis was 40 per cent in both groups. Infection occurred after a median of 9–10 days in eight patients in the therapy group and seven control patients. The clinical course using the Acute Physiology And Chronic Health Evaluation II score revealed a deterioration in the control group while in the therapy group a significant improvement could be observed ($P<0{\cdot}01$). The mortality rate in the control group was 15 per cent; no patient died in the therapy group

These results suggest that antibiotic prophylaxis cannot prevent or delay bacterial infection of pancreatic necrosis. However, it does significantly improve the clinical course when started before infection of necrosis has occurred.

Taking swabs at appendicectomy is valueless

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It is conventional to send a swab for microbiological culture at appendicectomy but the yield of organisms, even when the appendix is gangrenous or perforated, is less than 50 per cent.

Fifty-two consecutive patients, with subsequent histological confirmation of appendicitis, had a piece of appendix sent in holding medium for aerobic and anaerobic culture. All had metronidazole prophylaxis with or without cefuroxime In only four cases (8 per cent) were no organisms grown; a wide variation of yield was grown in the remainder.

A yield of Gram-positive cocci was significantly associated with preoperative systemic inflammatory response syndrome (SIRS) compared with other organisms (81 *versus* 29 per cent, $P<0{\cdot}001$) and tended to be associated with perioperative complications (57 *versus* 39 per cent, $0{\cdot}1<P>0{\cdot}05$) and a history of less than 24 h (57 *versus* 42 per cent, P not significant) The practice of sending a routine swab for microbiological analysis is valueless. If microbiology is important (patients with SIRS or gangrenous/perforated appendices), sending a piece of appendix is recommended.

Infection after hepatic resection in the elderly

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Ninety-seven patients older than 65 years of age underwent hepatic resection for malignancy ($n=91$) or benign disease ($n=6$). There were 39 men and 58 women with a mean(s.d.) age of 74(6) years. Primary neoplasia was the cause of resection in 35 patients, gallbladder cancer in 16 and metastatic disease in 40. The overall rate of major resection (three or more liver segments) was 73 per cent and the overall mortality rate was 14 per cent. Sixty-five postoperative complications were recorded in 42 patients and infection was the leading problem in nearly all of these patients (95 per cent). The histological type of tumour rather than the magnitude of resection had an influence on clinical mortality and morbidity rates. All complications occurred in patients with malignant disease ($P=0{\cdot}03$). Adverse effects on postoperative morbidity could be observed in adenocarcinoma of the hepatic ducts, gallbladder carcinoma and cholangiocellular carcinoma ($P=0{\cdot}003$). Intra-abdominal infections were found in 25 per cent of these patients and were due to biliary leakage in 58 per cent. Pneumonia was the leading complication associated with patient survival. All patients who developed pneumonia as a late complication during a complicated course died after operation ($P=0{\cdot}0001$). Severe preoperative liver dysfunction carried a significantly higher risk of postoperative morbidity and mortality ($P=0{\cdot}003$ and $P=0{\cdot}01$), which showed an incremental risk with age above 80 years ($P=0{\cdot}002$ and $P=0{\cdot}0004$). Right lobectomy and extended right lobectomy carried a significantly increased risk of postoperative morbidity ($P=0{\cdot}004$).

Infection is associated with nearly every complication recorded after hepatic resection in the elderly. Pneumonia as a late complication poses a worse prognosis in elderly patients who have undergone hepatic resection. Patients older than 65 years of age and especially those older than 80 years of age are more liable to succumb to complications which are predominantly infective.

Effects of nitroglycerin ointment on the healing of wound infection

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The effects of nitroglycerin ointment on the healing of infected wounds were investigated. Thirty mice underwent a midline abdominal incision including skin, subcutaneous fat, fascia and muscle, and staphylococcal coagulase-positive micro-organisms were applied to the wound. The incisions were closed primarily and the mice were divided into three groups of ten. In group 1 (control group) topical placebo was applied to wounds twice daily. In group 2 topical nitroglycerin ointment was applied to wounds twice daily beginning on the first day after wound closure In group 3 topical nitroglycerin ointment was applied to wounds twice daily beginning on the fifth day after wound closure.

Only three mice in group 1 died, one on the second and two on the third day after wound closure. On the tenth day after wound closure cultures were obtained from the wound, the mice were killed, and wounds were removed and examined histologically. In group 1 there were multiple abscess foci and severe infection extending to the subcutaneous fat and muscle in all mice. In group 2 there were multiple abscess foci in two mice and mild infection extending to the subcutaneous fat and muscle in six. In group 3 there were multiple abscess foci in two, severe infection extending to the subcutaneous fat and muscle in two, and mild infection in eight. In the cultures obtained from the wounds, coagulase-positive staphylococci were present in all mice in group 1, none in group 2 and only three in group 3.

It is concluded that topical nitroglycerin application has a beneficial effect on the healing of wound infection.

Kinetics of plasma interleukin 6, MRP, C-reactive protein (CrP) and endotoxin levels during aseptic surgery and peritonitis

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In ten patients undergoing cardiac surgery with cardiopulmonary bypass, endotoxin, CrP, MRP8, MRP14 and heterocomplex levels were determined during and after operation. MRPs are proteins derived from monocytes and granulocytes and are expressed during acute and chronic inflammation.

Endotoxin appears in the circulation at operation and decreases during the postoperative phase. CrP plasma levels increase until day 2 after operation which represents the end of the observation period. Similar changes occur in MRPs, except for MRP14 which is at its highest level on day 1. The same parameters were determined during the treatment of secondary peritonitis in seven patients. Even before operation levels of all parameters were raised significantly compared with normal values. However, there was a difference in patients who survived and patients who died exhibiting the heterocomplex. Furthermore, a statistically significant correlation was established between endotoxin and MRP14 in patients with peritonitis. This preliminary study gives an indication of the possible role of endotoxin translocation from the gut as a trigger of the postoperative acute-phase response. The MRPs are new measurable variables in the acute-phase response induced by surgical manipulation and infection as demonstrated in patients with peritonitis. Plasma levels of MRP seem to react faster than those of CrP and partially correlate with plasma levels of endotoxin. Further studies are needed to elucidate the diagnostic and prognostic relevance of MRPs.

Effect of multiple dose administration of trovafloxacin on bowel microflora in healthy men

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Trovafloxacin is a fluoronaphthyridone related to well known fluoroquinolone antibacterial agents, such as ciprofloxacin. Preclinical studies demonstrate that trovafloxacin possesses activity against Enterobacteriaceae, Pseudomonaceae, and Gram-positive bacteria, such as *Enterococcus faecalis*, and anaerobes, such as *Bacteroides fragilis*.

In a double-blind study, healthy male volunteers (aged 18–43 years, weight 59–92 kg) were randomized to receive trovafloxacin 200 mg, or placebo, once daily for 10 days. Microflora in homogenized faecal samples collected 1 week before, on days 0, 4, 7, 10 and 17 of dosing, and at follow-up 10–14 days later were determined.

Before treatment, the number of Enterobacteriaceae, aerobic Gram-positive cocci and anaerobes was similar in faeces obtained from subjects assigned to trovafloxacin ($n = 12$) and placebo ($n = 7$). No Enterobacteriaceae were detected in samples obtained on days 4, 7 and 10 in trovafloxacin-treated subjects, whereas in those receiving placebo ($n = 6$) no changes in Enterobacteriaceae were observed throughout the study. At day 17, recolonization with new Enterobacteriaceae was documented in the faeces of trovafloxacin-treated volunteers. In both trovafloxacin- and placebo-treated subjects, no differences in prevalence, appearance or disappearance of aerobic Gram-positive cocci, anaerobic bacteria or yeasts were observed. All Enterobacteriaceae tested were highly susceptible to trovafloxacin (minimum inhibitory concentration (MIC) 0·023–0·064 mg/l) before treatment and no increase in MIC was detected in *Escherichia coli* isolated on day 17 and at follow-up. *Clostridium difficile* was not detected at day 17 or at follow-up in samples obtained from trovafloxacin-treated subjects, and no *Clostridium* toxin was present.

These results indicate that trovafloxacin is able to decontaminate the bowel flora, but does not exhibit unfavourable effects.

Abdominal tuberculosis: diagnosis and surgical therapy in 139 cases

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Abdominal tuberculosis is a rare infection but the incidence is increasing. The non-specific signs and symptoms, and the laboratory and radiological techniques available, may be insufficient for its diagnosis. This delay in diagnosis and treatment leads to a high morbidity and mortality rate.

Between 1980 and 1996, 139 patients, 76 men (54·7 per cent) and 63 women (45·3 per cent) with abdominal tuberculosis were evaluated according to age, sex, history, physical examination and laboratory findings, diagnostic and therapeutic options, morbidity and mortality criteria. The mean age of the patients was 39·3 (range 11–72) years. The most frequent complaints and physical findings were abdominal tenderness (81·6 per cent), abdominal pain (71·4 per cent), weight loss, anorexia (60·2 per cent), ascites and fever. While ten patients (7·2 per cent) were diagnosed and treated by laparoscopic or endoscopic procedures, 114 (82·0 per cent) underwent laparotomy. Peritoneal tap and blind needle liver biopsies gave positive results. There were 67 cases of peritoneal tuberculosis (48·2 per cent), 46 (33·1 per cent) intestinal, 14 hepatic, five gastric, four splenic, two duodenal and one bile duct tuberculosis. Wound infection was the most common complication (19·6 per cent). Overall and emergency mortality rates were 10·8 and 23·5 per cent respectively.

Comparison of oral and parenteral perioperative antimicrobial prophylaxis with ciprofloxacin in colorectal and biliary tract surgery

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Postoperative infections following general surgery are complications with high associated mordidity and mortality rates. The best method of prophylaxis is still a matter of debate. Between December 1991 and August 1994, patients having elective colorectal or biliary tract surgery were randomly assigned to receive either ciprofloxacin 500 mg orally and two placebo infusions, or two infusions of ciprofloxacin 200 mg intravenously and one placebo tablet orally. Ciprofloxacin was administered once either 1 h before (oral) or immediately before (intravenous) the operation. The patients were observed for wound infection, other infections and side-effects for at least 8 days.

Some 420 patients were treated with ciprofloxacin, 209 orally and 211 intravenously. The mean(s.d.) age was 59·7(11·3) and 59·0(12·9) years in the oral and intravenous groups respectively. The groups did not differ significantly in terms of age, sex, weight, height and associated diseases. Some 249 colorectal procedures (122 oral, 127 intravenous) and 171 biliary tract operations (87 oral, 84 intravenous) were performed. The different operative procedures and the duration of operation did not differ significantly between the oral and intravenous groups. The prophylaxis of infection was assessed as follows: success (i.e. no infection), partial success (i.e. no wound infection but other infections not related to the operative procedure), failure (i.e. wound infection) and assessment not possible (antibiotic treatment before day 8 or death).

Assessment	Oral ($n = 209$)	Intravenous ($n = 211$)
Success	158 (75·6)	168 (79·6)
Partial success	29 (13·9)	25 (11·8)
Failure	5 (2·4)	2 (1·0)
Assessment not possible	17 (8·1)	16 (7·6)

Values in parentheses are percentages.

The efficacy of prophylaxis did not differ significantly between the oral and intravenous groups. In colorectal and biliary tract surgery, oral perioperative prophylaxis with ciprofloxacin is comparable to parenteral administration in terms of efficacy and safety

Early results of isotope granulocyte scintigraphy for detection of infected prosthetic vascular grafts

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The frequency of prosthetic vascular graft infection is relatively low, but in almost every case leads to severe bleeding and sometimes to the loss of a limb. The diagnosis of perigraft infection is difficult unless it is confirmed by a further complication Ten consecutive patients were examined from 1 to 4 years after implantation surgery of a prosthetic vascular graft with ^{111}In-labelled patient granulocytes (two aortobifemoral and eight femorodistal bypasses). The detection was performed by a modified two-phase technique, at 1 h and 3 h after injection. The mean(s.d) leucocyte uptake index was calculated as 1·8(0 3) (1 h after injection).

Eight infections were detected by 1 h after injection. After one reconstruction of an infected pseudoaneurysm within a short period of time after operation, a new aneurysm occurred but in that case leucocyte uptake was not present in blood.

It is suggested that false-positive results are observed rarely. Of eight infected grafts proven by positive isotope-labelled leucocyte uptake index, the samples taken from fluid in the perigraft region during surgery contained bacteria in six and were negative in two. Comparison with ultrasonography or angiography showed that the leucocyte scan is able only to verify perigraft infection.

Operative management of intra-abdominal abscesses

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Interventional computed tomography (CT) and ultrasonographically guided abscess drainage are increasingly being performed. To define the recent role of open surgery in the treatment of intra-abdominal abscess, the authors retrospectively reviewed 93 patients who were operated on between January 1985 and November 1995. One group of 38 patients had primary abscesses associated with Crohn's disease, appendicitis and pancreatitis, another group of 55 patients had had a previous operation Eight patients had open surgery after CT-guided drainage failed Seventy-one abscesses (76 per cent) were single, 22 patients had multiple abscesses

Successful drainage by a single surgical procedure was achieved in 74 patients (80 per cent) Twenty per cent required reoperation for recurrence of the abscess or abscess-related complications Minor complications such as bleeding and wound infection were seen in 16 per cent. The overall mortality rate was 20 per cent (19 patients), mostly because of septic multiorgan failure. The mortality rate was more than twofold greater when repeated drainage was necessary (nine of 19 patients). Pancreatic abscess and severe sepsis, documented by a high Acute Physiology And Chronic Health Evaluation II score, seem to be indications for open surgery. It is concluded that operative drainage plays an important role in the therapy of intra-abdominal abscess The partnership of intensivist, radiologist and surgical consultant has to decide on the most suitable technique according to location and clinical course. Successful primary drainage is essential for a favourable outcome.

Critical re-evaluation of antibiotic-related cardiovascular instability in general surgery: complex interaction and overall usefulness

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Cardiovascular instability following antibiotic prophylaxis in general surgery is thought to be of a histamine-related anaphylactoid type. A more complex interactive process may be involved and has prompted a reinvestigation of the problem in a prospective randomized clinical trial. Some 240 representative patients were randomly allocated to four treatment groups receiving either H_1H_2 antihistamines or placebo as well as Haemaccel *versus* Ringer solution after induction of anaesthesia before surgery, 114 subjects received prophylactic antibiotics (cefuroxime–metronidazole) as indicated clinically. Cardiovascular instability was recorded carefully by an independent monitor; histamine was measured at defined time intervals.

Twenty-eight of 114 patients had antibiotic-related cardiovascular instability; episodes in nine of 114 were clinically relevant and three were histamine associated. A slight negative trend was observed for all groups receiving antihistamine prophylaxis (19 of 114 events with antihistamines *versus* nine of 114 without antihistamines) Further analysis identified lack of prophylactic colloid volume loading as the most important factor favouring clinically relevant hypotension ($P<0{\cdot}05$). Most cardiovascular instability following antibiotic prophylaxis was not histamine related and was not influenced positively by antihistamines which were necessary to cope with side-effects of colloids after induction of anaesthesia Colloids diminished antibiotic-related hypotension.

Consideration of the complex interaction of several prophylactic measures (antihistamines, antibiotics, volume loading) needs to be the mandatory approach for calculating their usefulness in patient recovery.

Diffuse peritonitis: comparison of planned reoperation and revision on demand

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Reoperations, whether planned or 'on demand', are well established concepts in the management of severe diffuse peritonitis. Both concepts were applied and reviewed with regard to major complications and mortality rate.

Between 1 January 1989 and 31 May 1994, 62 patients with the diagnosis of diffuse peritonitis underwent operative treatment. The mean age of 29 female and 33 male patients was 58·2 (range 17–93) years The origin of the peritonitis was the stomach in 81 per cent, duodenum in 16 per cent, small intestine in 13 per cent, large intestine in 42 per cent and the pancreas in 16 per cent. Of the 62 patients, 15 were reoperated on according to plan and 47 underwent reoperation on demand.

The Mannheim peritonitis index calculated at operation and the Acute Physiology And Chronic Health Evaluation (APACHE) II score were similar in both groups and so was mortality rate. The mean number of reoperations was five in the group of planned revisions and three in the group of on-demand revisions. Regarding deaths, only the patients' age ($P<0{\cdot}03$) and the preoperative APACHE II score ($P<0{\cdot}01$) reached statistical significance As expected, eradication of the infectious source was the precondition of survival regardless of the type of reoperation.

It is concluded that planned or on-demand reoperations lead to similar results in the operative treatment of diffuse peritonitis. The crucial point for success is that elimination of the source of infection takes place as soon as possible

Analysis of a methicillin-resistant *Staphylococcus aureus* outbreak in a surgical ward

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In October 1995 an increase was noticed in the number of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates from clinical specimens sent to the microbiology laboratory from a surgical ward. To analyse this outbreak, all MRSA isolates obtained from clinical specimens of this surgical ward were collected prospectively for 10 weeks (14 MRSA isolates from wound cultures of ten patients). It was found that all patients had postoperative MRSA wound infection and the mean interval from admission to the first MRSA isolate was 34·5 (range 20–53) days. During this period all patients received intravenous or oral sulbactam–ampicillin, or a first-generation cephalosporin (mean duration 25 (range 7–60) days). Nine patients had multiple hospital admissions and multiple operations for congenital anomalies, burns or trauma. One patient was operated on for malignancy. Surveillance cultures were taken from ward personnel (nose cultures from four physicians, seven nurses, one secretary and one waiter), two surgical dressing containers and nebulizers.

Three physicians, three nurses and a secretary were found to be nasal MRSA carriers. MRSA was isolated from one surgical dressing container and nebulizer. To identify the source of the outbreak and demonstrate the clonal relationship between MRSA isolates arbitrarily primed-polymerase chain reaction (AP-PCR) was used AP-PCR analysis showed that most of the MRSA isolates belonged to two major clones (pattern A and pattern B). Pattern A was the most frequent and was present in four clinical isolates and the surgical dressing container Pattern B was identified in three clinical isolates and a nose culture of one physician. Patterns closely resembling pattern A (pattern A^{1}) and pattern B (pattern B^{1}) were detected in one clinical isolate and the nose culture of one physician, and in one clinical isolate and the nose culture of a nurse respectively. Band patterns of the remaining MRSA isolates were completely different. It was thought that this MRSA outbreak was caused by the contamination of surgical dressing containers with MRSA and nasal MRSA carriage in ward personnel.

Endotoxin enhances *in vitro* platelet aggregability in whole blood

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There is little information about the influence of endotoxin on platelet aggregability. It has been shown that endotoxin directly stimulates platelets via protein kinase C, but may be mediated by monocytes and/or neutrophils. Most tests used for investigation of platelets are performed using platelet preparations. Impedance aggregometry in whole blood offers the chance of quantifying platelet aggregability including the interaction with other blood cells.

Blood from eight healthy volunteers (four female, four male) was drawn into tubes containing 3·8 per cent buffered sodium citrate. Endotoxin from *Escherichia coli* (0127·B8) was added at a final concentration of $1\ \mu\text{g ml}^{-1}$, samples without endotoxin served as controls Platelet aggregation was tested using whole blood electrical aggregometry. Adenosine 5′-diphosphate (ADP) $10\ \mu\text{mol l}^{-1}$, collagen (COL) $5\ \mu\text{g ml}^{-1}$ and arachidonic acid (AA) $500\ \mu\text{mol l}^{-1}$ were used as agonists. The integral of aggregation curves was used for quantification

Endotoxin alone was not able to trigger platelet aggregation in whole blood, whereas endotoxin in combination with ADP or COL significantly enhanced platelet aggregation compared with controls ($P<0{\cdot}0012$; $P<0{\cdot}017$) Endotoxin in combination with AA led to a non-significant enhancement Although stimulation of platelets by endotoxin has been reported, platelet aggregation in whole blood was not observed with endotoxin alone. Endotoxin in combination with agonists enhanced platelet aggregation. Two possible explanations can be proposed: (1) endotoxin leads to a prestimulation, enhancing subsequent aggregation to agonists; (2) endotoxin activates monocytes producing proaggregatory substances like platelet-activating factor, thromboxane A_2 or cathepsin G

Prevention of bacterial translocation in acute pancreatitis

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Bacterial translocation has been reported following the induction of pancreatitis using the choline-deprived and ethionine-supplemented (CDE) diet model in mice. Studies of host defence function suggest that infections are associated with a fall off in neutrophil and macrophage function. Granulocyte–macrophage colony-stimulating factor (GM–CSF) is known to modulate the activity of neutrophils and macrophages This study evaluated the possibility of prevention or reduction of bacterial translocation in a non-invasive experimental model of acute pancreatitis.

Acute pancreatitis was induced in CD1 female mice (12–14 g) using a CDE diet at dose of DL (lethal dose) 50 and DL100. Samples of mesenteric lymph nodes, liver, spleen, pancreas and lung were obtained for bacteriological analysis. Prevention of bacterial translocation was tested with saline infusion (0·03 ml per g per day). Some 103 mice were divided into six groups: (1) fed normally, (2) starved, (3) CDE DL50, (4) CDE DL50 plus saline, (5) CDE DL100 plus saline and (6) CDE DL100 plus saline plus GM-CSF (1 ng per g per day).

The mortality rate was 0, 0, 55, 24, 74 and 61 per cent in groups 1–6 respectively. Bacterial translocation was present in normally fed (2 per cent) and starved (10 per cent) animals and was promoted in the CDE DL50 group (19 per cent). Saline infusion decreased bacterial translocation in mice fed CDE DL50 (4 per cent; $P<0{\cdot}005$). Bacterial translocation was directed in 56 per cent of resuscitated mice in the CDE DL100 group; in this condition GM-CSF significantly reduced bacterial translocation to 11 per cent ($P<0{\cdot}01$)

Acute pancreatitis promotes bacterial translocation. Resuscitation may reduce bacterial translocation but treatment with GM-CSF may restore the impaired capacity of response to an aseptic stimulus and further reduce bacterial translocation.

Taurine supplementation modulates murine peritoneal macrophage function

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Taurine enhances human macrophage antimicrobial activity, and it is established that sepsis depletes plasma taurine The effect of taurine supplementation on peritoneal macrophage activation was evaluated in a murine model of sepsis.

CD-1 mice were randomized into three groups: (1) controls ($n=8$); (2) lipopolysaccharide (LPS) $25\ \text{mg kg}^{-1}$ ($n=16$); and (3) caecal ligation and puncture (CLP) ($n=16$). Eight mice from groups 2 and 3 received 4 per cent taurine in the drinking water for 5 days before induction of sepsis Twenty-four hours after insult, peritoneal macrophages were assayed for tumour necrosis factor (TNF) α, nitric oxide and superoxide anion.

CLP significantly raised TNF-α levels and this was attenuated by taurine (mean(s.d.) 54·8(11 9) *versus* 17 5(6·7) pg ml^{-1}). Taurine also signficantly increased superoxide production following CLP (18(2) *versus* 31(3) pmol per well). However, supplementation had no effect on TNF-α or superoxide release in the LPS group.

Taurine confers immune benefits in a CLP model of sepsis by enhancing antimicrobial function as assessed by superoxide production, whilst downregulating the proinflammatory cytokine TNF-α.

Effects of granulocyte colony-stimulating factor on septicaemia in diabetic rats

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Diabetic patients are more prone to infection and the evidence for an immunological defect superimposed upon the metabolic abnormalities of diabetes is convincing. Neutrophils play a critical role in the host defence mechanism against various bacterial infections, and it is suggested that impaired neutrophil function causes susceptibility to infection in diabetic patients. To explore the possibility that granulocyte colony-stimulating factor (G-CSF) may be useful in preventing the morbidity and mortality caused by infections in diabetics the effect of G-CSF against septicaemia was studied in diabetic rats.

Forty-eight rats were divided into seven equal groups. Groups 4–7 were made diabetic by intraperitoneal injection of streptozotocin. Groups 4, 6 and 7 were made septicaemic by caecal ligation and perforation at the end of the second week of streptozotocin injection. G-CSF was injected subcutaneously into rats in groups 3, 5 and 6. White blood cell counts, and neutrophil counts and function, were determined. Rats in all groups were observed for 7-day survival.

White blood cell, neutrophil and lymphocyte counts and the neutrophil phagocytosis index decreased but the neutrophil adherence rate was not different in group 2 ($P<0{\cdot}05$). All these variables were significantly diminished in group 4 ($P<0{\cdot}05$). G-CSF injection improved all variables except neutrophil adherence. The cumulative survival ratio was better in group 6 than in group 7 ($P<0{\cdot}05$).

In conclusion, G-CSF increased neutrophil counts, developed neutrophil functions and improved survival. These data suggest that G-CSF may be useful as a drug to prevent bacterial infection in diabetic patients

Role of diltiazem in preventing bacterial translocation in obstructive jaundice

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Surgery in patients with obstructive jaundice is associated with significant infective complications probably due to the passage of viable bacteria from the gastrointestinal tract to extraintestinal sites, such as the mesenteric lymph nodes (MLNs), liver, spleen and blood. The present study investigated this and also determined whether diltiazem has any effect on bacterial translocation in obstructive jaundice.

Thirty male Sprague–Dawley rats were anaesthetized with ether and allocated to three groups (ten in each): sham operation (group 1) or common bile duct ligation and transection (groups 2 and 3). Ten rats forming the study group (group 3) received diltiazem $400\,\mu g$ per kg body-weight intravenously for 7 days, starting 3 days after operation. Animals in group 2 received an equal volume of isotonic saline for the same period. All animals were killed on the tenth day and tissue cultures were obtained from the MLNs, liver and spleen Cultures were also made from the blood and caecal content A piece of liver and terminal ileum were removed for histopathological examination, and blood samples for liver function tests were obtained.

The rates of bacterial translocation to MLNs, liver and spleen in jaundiced saline-treated animals (60, 70 and 50 per cent respectively) were significantly higher ($P<0{\cdot}05$) than those in both sham-operated controls and the other jaundiced animals treated with diltiazem (0 per cent in group 1, and 0, 20 and 10 per cent respectively in group 3). In jaundiced groups there was also a statistically significant increase in the caecal bacterial content when compared with non-jaundiced sham-operated controls ($P<0{\cdot}01$).

The data suggest that administration of diltiazem can prevent jaundice-associated bacterial translocation. Studies on humans are needed to demonstrate similar clinical effects of diltiazem.

Intraductal antibiotic prophylaxis in endoscopic retrograde cholangiopancreatography: evaluation of clinical experience by an animal study

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To avoid hepatobiliary and/or pancreatic duct infection during endoscopic retrograde cholangiopancreatography (ERCP) the authors enrich the contrast medium with imipenem (imipenem $5\ mg\ ml^{-1}$, jopamidol $200\ mg\ ml^{-1}$). An intraluminal surgical endoscopic intervention is performed in about 65 per cent of their surgical patients. This good clinical experience was the reason for carrying out an animal study to show the benefit of intraductal antibiotic prophylaxis in ERCP.

In 23 minipigs tissue concentration and plasma concentration was measured after administration of intraductal intravenous antibiotics After laparotomy the cystic duct was ligated and selective papillary intubation was possible after duodenotomy. A standardized antibiotic dose related to animal weight was given.

The plasma concentration of antibiotic was similar after intraductal and intravenous application, but with intraductal application the tissue concentration was three times higher than by intravenous treatment. Significant enteral reabsorption of imipenem was excluded by measurement in two individuals. No toxic or allergic reaction to imipenem was seen either in the animal experiment or in clinical experience.

Intraductal antibiotic prophylaxis is sufficient to minimize problems of infection after interventional ERCP In cases of good biliary run-off the physiological bacterial spectrum of other mucosal regions is not suppressed.

D-Lactate as a marker for intestinal ischaemia after abdominal aneurysm repair

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Patients with acute ruptured abdominal aortic aneurysm (AAAA) are at risk of developing intestinal ischaemia after surgery, but it is difficult to diagnose this ischaemia at an early stage. D-Lactate is produced in increased amounts by intestinal bacteria after ischaemia and in cases of short bowel disease. L-Lactate is a product of all cells, produced in hypoxia by anaerobic metabolism, and could be used as a specific marker for intestinal ischaemia after AAAA.

Twenty-one patients with AAAA were divided retrospectively into two groups with and without intestinal complications, as verified with endoscopy. As controls, four patients with ventilation-associated pneumonia were included with six healthy subjects. Blood was taken on admission to the intensive care unit, centrifuged and frozen until measurement. Levels of D-lactate below $0{\cdot}1\ mmol\ l^{-1}$ and L-lactate below $2{\cdot}0\ mmol\ l^{-1}$ are considered to be normal. D-Lactate was significantly increased ($P<0{\cdot}05$) in patients with intestinal ischaemia after acute aneurysm repair

In critically ill patients D-lactate, but not L-lactate, measured on admission, was predictive of later intestinal ischaemia.

Burn–sepsis-induced bacterial translocation: role of loss of hepatic arterial buffer response and portal hypertension

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Alteration in the hepatic circulation after injury appears to be an essential component in the development of multiple organ distress syndrome. Hepatic ischaemia–reperfusion injury may account for systemic spillover of indigenous bacteria or endotoxin. In this study, the impact of burn and endotoxin in the hepatic arterial buffer response was investigated.

Female pigs ($n = 12$, 20–25 kg) were fitted with ultrasonic flow probes on the portal vein and the common hepatic artery, and a catheter in the superior mesenteric vein. After 5 days all animals were anaesthetized and six of them received a tertiary burn of 40 per cent total body surface area. *Escherichia coli* lipopolysaccharide (LPS) 100 μg kg^{-1} was administered intravenously at 18 h. All animals were studied for 42 h.

The portal blood flow was significantly reduced for a period of 8 h after endotoxin (51 per cent of baseline; $P<0\cdot05$, analysis of variance). The hepatic arterial blood supply was also significantly reduced (mean(s.d.) 26(16) *versus* 215(12); $P<0\cdot05$) during the first 4 h after endotoxin, indicating loss of the hepatic arterial response. In the following 12 h a hepatic reperfusion phase was observed, with an increase in the hepatic artery blood flow to 152 per cent of baseline value ($P<0\cdot05$). Although the burn injury did not affect the portal venous pressure, the portal blood flow showed an increase of 32 per cent 1 h after the burn. Endotoxaemia after the burn caused a significant portal hypertension over a period of 8 h (mean(s.d.) 36(2) *versus* 17(2); $P<0\cdot05$). Bacterial translocation occurred in five of six animals in the burn–LPS group in comparison with one of six sham-treated pigs ($P<0\cdot05$, Fisher's exact test).

In sepsis after burning, the hepatic arterial blood flow is significantly reduced independently of alterations in portal venous blood flow, indicating dysregulation of the physiology of the hepatic arterial buffer response. This selective hepatic ischaemia, together with the observed portal hypertension, may account for bacterial translocation, by diminishing hepatic bacterial clearance capacity and damaging the intestinal mucosal barrier.

Role of endothelin in obstructive jaundice

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Obstructive jaundice is often complicated by renal impairment and complications associated with sepsis due to an impaired immune system. The pathophysiology and the mediators taking a role in this phenomenon are poorly defined. In this study, the role of endothelins in obstructive jaundice was investigated in rats

The distal common bile duct was ligated for 7 days in two groups of rats. While the control group ($n = 7$) received no medication, others ($n = 8$) received Bosentan (a non-specific endothelin A and B receptor antagonist) 50 mg kg^{-1} orally for 10 days. There was also a sham-operated group. On the seventh day endothelin levels were measured in the infrahepatic vena cava in addition to serum bilirubin, creatinine and alkaline phosphatase levels. Hyaluronic acid (HA) and β-*N*-acetyl hexosaminidase (β-NAH) levels were also measured in this sample. Glutathione (GSH) levels were determined in liver tissue.

Endothelin levels increased significantly in the control group (mean 50·5 pg ml^{-1}) when compared with sham-operated rats (13·8 pg ml^{-1}) ($P = 0\cdot008$), Bosentan prevented the increase in endothelin level in bile duct-ligated rats (28·7 pg ml^{-1}). HA, β-NAH, bilirubin, creatinine and alkaline phosphatase levels increased and GSH levels decreased significantly in the control group. Bosentan prevented GSH consumption. Although HA and β-NAH levels decreased with Bosentan the difference was not significant. Endothelin appears to be an important mediator in obstructive jaundice. The endothelin receptor antagonist Bosentan prevents an increase in endothelin level in serum and prevents tissue damage. Endothelins may be responsible for the renal and immune system impairment in obstructive jaundice.

Bosentan prevents colonic injury in experimental colitis

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Several mechanisms are involved in the pathogenesis of chronic inflammatory bowel disease. This study determined the role of endothelins in experimental colitis.

Colitis was induced by intracolonic administration of trinitrobenzene sulphonic acid in 0·5 ml 50 per cent ethanol in Wistar–Albino male rats (200–280 g). In the vehicle (VHL) group, animals received an ethanol enema, while rats in the control group (CNT) received no intracolonic instillation. Following the induction of colitis, rats were given orally either Bosentan, a non-selective endothelin receptor antagonist (100 mg kg^{-1}) (ABS group), or gum gum (ACL group) by gavage for 2 days. Two other groups of rats were given Bosentan or gum arabic for 14 days (CBS and CCL groups respectively). On the third day animals from the ACL and ABS groups, and on the 15th day animals from CCL and CBS groups, underwent laparotomy followed by excision of the whole colon. After performing macroscopic damage scoring, blood was withdrawn from the portal vein for the determination of plasma protein oxidation (PO) level and a distal colonic segment was kept for the determination of myeloperoxidase (MPO) activity and histological assessment

Mean(s.d.) MPO activities of colonic tissues were raised in the ACL and CCL groups (325·1(44·9) and 431·8(54·6) units per g wet weight) compared with the CNT group (73·6(11·0) units per g wet weight). Mean(s.d.) PO levels were found to be significantly increased in the CCL group (1158·1 (63·4) nmol ml^{-1}) compared with CNT and VHL groups (274·3(23·1) and 490·0(52·2) nmol ml^{-1}). Bosentan treatment significantly reduced both the PO level (375·5(46·9) nmol ml^{-1}) and MPO activity (167.5(35·8) units per g wet weight) in the CBS group with respect to the CCL group. Mean(s.d.) macroscopic lesion indices of the colon were assessed as 0, 1·4(0·4), 4.8(0·6), 3·0(0·5), 3·8(0·3) and 2·3(0·5) in CNT, VHL, ACL, ABS, CCL and CBS groups respectively. Histologically, there was a wide range of severe inflammation in the ACL and CCL groups, whereas the findings of mild inflammation in the ABS and CBS groups were consistent with damage prevention.

The results of the present study indicate that the inhibition of endothelin receptors results in prevention of ulcer formation and a reduction in the colonic inflammatory response. Endothelins may be involved in the pathogenesis of colonic injury in this animal model of chronic colitis.

Heparin coating reduces the inflammatory responses based on activation of CD14-positive cells

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Activation of circulating cells is an important part of the inflammatory response. The result of this activation is release of cell products like proteolytic enzymes and several proinflammatory cytokines The membrane protein CD14 on monocytes and macrophages acts as a receptor for several activators including the complex of endotoxin bound to lipopolysaccharide binding protein in plasma. Activation of CD14 subsequently activates an intracellular signal cascade, which acts by stimulating the messenger RNA (mRNA) synthesis of different mediators

Monodisperse paramagnetic beads covered by CD14 antibodies have been used to isolate CD14-positive cells (monocytes/macrophages) from whole blood In *in vitro* experiments a venovenous bypass was used as a model to study whether coating the inner surface of the bypass circuit with covalently bound heparin is important for biocompatibility, measured by activation of CD14-positive cells and production of cytokines In ten experiments, all parts of the perfusion circuits were heparin coated, whereas in ten other experiments non-coated systems were used. As a control for spontaneous cell activation, blood was incubated in the same sets of tubing at 37·5°C without circuit flow but with rotation. Blood samples were collected at time intervals for 48 h and CD14-positive cells were isolated. Further, oligo(dT)$_{25}$ beads (Dynal) were used to isolate mRNA, before subsequent reverse transcriptase–polymerase chain reaction on different cytokines (tumour necrosis factor α, interleukin (IL) 1β, IL-2, IL-6, IL-8 and IL-10).

These data show that, in contrast to the bypass circuit with covalently bound heparin, the non-coated circuits strongly upregulated the mRNAs for proinflammatory cytokines IL-1β and IL-6. In addition, IL-1β and IL-6 protein measured in plasma by enzyme-linked immunosorbent assay reflected the upregulated mRNAs. This indicates that heparin represents a biologically active surface that reduces cell activation

Inhibition of inducible nitric oxide synthase by aminoguanidine attenuates endotoxin-induced decrease in mesenteric blood flow

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The study investigated the effects of the inhibition of inducible nitric oxide synthase on endotoxin (ET)-induced decreased mesenteric blood flow (MBF). Sprague–Dawley rats were given either saline 1 ml kg^{-1} or *Escherichia coli* ET 1 mg kg^{-1} intraperitoneally and also treated with either aminoguanidine (15 mg kg^{-1} intraperitoneally 20 min before and 2 h after ET injection) or its solvent saline 0·1 mg kg^{-1}. Four hours after ET injection, animals were anaesthetized with sodium pentobarbitone, carotid arteries were cannulated and mean arterial blood pressure (MABP) was recorded MBF was recorded by transonic perivascular flow probes and mesenteric arterial resistance was calculated. Vascular responsiveness to phenylephrine (1–100 μg kg^{-1} intravenously, cumulative) was also investigated

ET did not significantly affect the MABP but decreased the mean(s.d.) MBF (controls 13·9(1·5) ml min^{-1} ($n = 5$); ET 6.1(1.0) ml min^{-1} (n = 5); $P = 0·016$) by increasing the vascular resistance (controls 7·8(1·0) mmHg min ml^{-1}; ET 13·7(1·7) mmHg min ml^{-1}; $P = 0·0099$) Aminoguanidine had no effect on either the MABP or MBF but it completely blocked the effects of ET (e.g. MBF: aminoguanidine + saline 13·0(1·9) ml min^{-1}, aminoguanidine + ET 13·6(1·3) ml min^{-1}). On the other hand, ET significantly attenuated the responsiveness to phenylephrine while aminoguanidine restored it (mean(s.d.) decease in MBF in response to phenylephrine 10 μg kg^{-1} saline + saline 42·2(6·6) per cent; ET + saline 13·9(5·2) per cent; saline + aminoguanidine 32·4(8·1) per cent; ET + aminoguanidine 38·3(5·6) per cent).

These results indicate that ET decreased MBF by increasing the vascular resistance and decreased the responsiveness to phenylephrine, while the effects of ET were blocked by aminoguanidine. These findings suggest a potential use of inducible nitric oxide blockers in septic shock.

Perioperative results after thoracic operations with standardized antibiotic prophylaxis with cefotaxime

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Perioperative infections in thoracic surgery can cause problems. This retrospective study evaluated the postoperative outcome in terms of infective complications. All patients were given standard antibiotic prophylaxis using cefotaxime. There were 71 per cent men and 29 per cent women, mean age was 56 years. Some 40 per cent had pre-existing pulmonary disease, 47 per cent were smokers, 14 per cent had renal insufficiency and 28 per cent had obstructive or restrictive reduced lung function; 6 per cent had had previous thoracic operations. The indication for operation was malignancy in 64 per cent and infective disease in 10 per cent.

Mean length of admission was 21 days, stay in the intensive care unit 2·1 days and mean operating time 118 min. Lobectomy was performed in 36 per cent, bilobectomy in 4 per cent, pneumonectomy in 6 per cent, segmentectomy in 3 per cent, wedge resection in 16 per cent, enucleation in 10 per cent, VATS in 13 per cent and other procedures in 12 per cent. None of the patients died during or after operation. Mean duration of antibiotic use was 6·2 days After operation there were infections in nine patients (4 per cent): wound infection ($n = 4$), pneumonia (n = 1) and others ($n = 4$). In four patients there was resistance: *Xanthomonas* ($n = 2$), *Pseudomonas* ($n = 1$) and *Staphylococcus epidermidis* ($n = 1$), and in one an allergic reaction to cefotaxime. In 4 per cent reoperation was necessary but not because of infection.

It has been shown that performance of thoracic operations under perioperative antibiotic prophylaxis with cefotaxime is safe and has a low incidence of intraoperative and postoperative infections

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Correspondence

Reduced long-term survival following major peptic ulcer haemorrhage

Sir

This study (*Br J Surg* 1997; 84: 265–8) draws attention to the consequences (non-fatal and fatal peptic ulcer recurrence) of allowing the preoccupation with surgical procedures that alleviate life-threatening complications to dominate clinical decision-making, to the exclusion of strategies (medical or surgical) that modify favourably the natural history of peptic ulcer disease. The recognition that the peptic ulcer diathesis is one characterized by a relapsing course, even in the modern therapeutic era[1], mandates the implementation of strategies to reduce the recurrence rate, regardless of the immediate success of measures such as endoscopic haemostatic therapy. The prophylactic range includes, respectively, eradication of *Helicobacter pylori* in patients with proven infection[2] and long-term use of antisecretory therapy in those who are *H pylori*-negative[3]. A case could even be made for a 'belt and braces' strategy, using both treatments, in high-risk subgroups such as the elderly and those with serious co-morbidity. Even after successful eradication of *H pylori* 4–6 per cent of peptic ulcers recur[4] and sometimes with haemorrhagic sequelae[2]. For those with co-morbid disorders necessitating co-prescription of non-steroidal anti-inflammatory drugs (NSAIDs), misoprostol is preferable to H_2-receptor antagonists as it protects the duodenum (the only site protected by ranitidine)[5] and the stomach[5], the site most favoured by NSAID-related ulcers[6]. For those intolerant of the optimum recommended dose of 200 μg four times daily, modest prophylactic benefit, with significantly fewer side-effects, can still be obtained with a 50 per cent dose reduction[7].

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Double stapled transabdominal anastomosis for one-stage resection of acute sigmoid volvulus

Sir

Are all newly trained coloproctologists to be lost without a stapling gun? This paper (*Br J Surg* 1997; 84: 83–4) appears to offer little or no benefit over a one-stage handsewn colo-colostomy as recently reported from Ghana[1], where the patients were no doubt more compromised as one-half had gangrenous bowel. Stapling procedures are expensive and for this reason the technique would be inapplicable in many countries where *The British Journal of Surgery* is read.

Although the *BJS* appears to support ingenious applications of technology, for example, the novel inexpensive Libyan description of the use of an umbilical cord clamp[2], this paper seems to represent a description of a known mechanism of anastomosis in a new setting. With the advent of the MRCS examination, basic surgical skills courses and anastomosis workshops, we would favour greater emphasis on handsewn techniques and more widely applicable innovations.

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A better bridge for loop stomas

Sir

The recent flurry of correspondence regarding the optimal support for loop stomas (*Br J Surg* 1996; 83: 365, 1011, 1161, 1656, 1797) highlights the difficulties associated with external mechanical bridges. Fortunately, these are unnecessary Loop colostomies can be supported by fascial bridges secured with two or three interrupted sutures. Loop ileostomies require no bridge. We have performed over 400 loop ileostomies without bridges for ileal pouch diversion and several hundred more for diversion of distal large bowel anastomoses. While we have seen several cases of late stoma retraction, none has required surgical revision and none was felt to be attributable to a deficiency of foreign material beneath the bowel loop The afferent limb of the stoma is supported adequately by the everting sutures. A mechanical device for loop stoma support is a bridge too far.

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Surgery for biliary obstruction by tumour thrombus in primary liver cancer

Sir

Parenchymal insufficiency or failure is the cause of jaundice in most patients with an underlying primary liver cancer. Hepatoma presenting as obstructive jaundice is rare Unlike Tantawi and colleagues (*Br J Surg* 1996; **83**. 1522–5), we have found endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography, if ERCP failed, to be extremely useful in delineating the pathology. In our series of 48 patients with obstructive icteric type hepatocellular carcinoma, we have found the cholangiographic appearance very helpful in determining the need for further imaging Patients with a cholangiogram showing features of extraluminal compression of the hepatic ducts at the confluence or at the common hepatic duct invariably have inoperable disease due to tumour encasement of the ducts or malignant lymphadenopathy at the porta hepatis compressing the ducts. A proportion of patients with a common bile duct (CBD) filled with blood clots from haemobilia, or with a cholangiogram showing intraductal tumour thrombus with or without tumour fragments in the CBD, do have operable underlying lesions with a potential of cure. These patients warrant further imaging with computerized tomography and hepatic angiography to assess operability.

In patients with favourable cholangiograms, we relieve the obstruction by placing a plastic stent or a nasobiliary drain. If ERCP stenting fails, a percutaneous transhepatic biliary catheter is placed. We would advise against the placement of an expandable metal stent (for example, Wallstent) in these patients unless the lesion is definitely inoperable. The presence of a metal stent can make subsequent resection difficult.

Intraductal extension of hepatic cholangiocarcinoma is not surprising as cholangiocarcinoma is an adenocarcinoma that arises from the epithelium of the bile ducts Hepatoma arises from hepatocytes and the hepatoma has to invade into the bile duct before the tumour can propagate along the ductal lumen. At our institution, we differ from Tantawi and colleagues by regarding obstructive icteric type hepatoma as a different entity to cholangiocarcinoma obstructing the hepatic confluence.

We agree with Tantawi and colleagues that surgery for biliary obstruction by tumour thrombus can provide good and worthwhile palliation or even cure for a proportion of these patients

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Authors' reply

Sir

We fully agree with the comments of Messrs Leow and Lau about biliary obstruction by tumour thrombus complicating hepatocellular carcinoma. These authors note that patients with cholangiocarcinomas were included in the same study. In fact only patients with intrahepatic (peripheral) cholangiocarcinoma were included. In those patients, although histological examination showed biliary adenocarcinoma, the tumour presented as an intrahepatic mass in which the biliary origin is not assessable at surgical examination. It may even be difficult to differentiate intrahepatic cholangiocarcinoma from secondary liver cancer[1] In two patients with this tumour we observed biliary obstruction from tumour thrombus of the same type as hepatocellular carcinoma, that is, tumour debris non-adherent to the bile duct walls progressing along the lumen and obstructing it without invading it. It poses the same diagnostic and therapeutic problems as in patients with hepatocellular carcinoma, as resectability may be difficult to assess and it requires, in addition to liver resection, bile duct exploration, clearance and drainage. For these reasons these patients were reported with those of hepatocellular carcinoma.

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1 Cherqui D, Tantawi B, Alon R *et al.* Intrahepatic cholangiocarcinoma. Results of aggressive surgical management. *Arch Surg* 1995, **130**· 1073–8

Mesodiverticular band: a cute little bleeder

Sir

You will be having cartoons next

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Pilonidal sinus: experience with the Karydakis flap

Sir

We congratulate Mr Kitchen on his good results in the treatment of pilonidal sinus and especially in those with recurrent disease (*Br J Surg* 1996; **83**. 1452–5). The author's thoughts about the optimal surgery for eliminating the sinus and its predisposing factors are helpful in the understanding of this disease and its treatment. These thoughts differ, however, from the flap technique the author used. First, Mr Kitchen stresses the importance of avoiding crossing the midline with wound edges. He suspects this is the cause for early recurrence. In resecting a larger sinus, however, which straddles the midline he has to cross the midline as shown in *Fig 5*. Second, he explains correctly that the depth of the natal cleft is one of the major predisposing factors. By covering the resection defect with an undermined medial wound edge 1 cm thick, he creates a new, even deeper, cleft that is only deviated slightly from the midline as shown in *Figs 3* and *4*. We agree with the aim of keeping the suture line away from the natal cleft, but think there are other ways of achieving this. Mr Kitchen recommends (*Fig 1*) a generous resection of the lateral wound edge to create a well lateralized wound. This excises the healthy unaffected lateral part that pulls the suture line laterally and creates excessive tension on the wound. The medial-affected wound edge is resected only marginally and this wastes healthy unaffected tissue at the lateral wound edge and puts tension on to the wound. To avoid these unpleasant limitations of the Karydakis flap technique we recommend the modified fasciocutaneous V–Y-advancement flap[1]. With this flap there are fewer limitations for the necessary debridement and a safe medial-centred resection can be performed Defects up to 10 cm in diameter can be closed with this technique and the local anatomy has to be altered, i e. of flattening the deep natal cleft to a shallow groove. The key in avoiding recurrence lies in the modification of the usual V–Y-advancement flap design. A wide skin strip on the medial flap side is de-epithelialized. This part of the flap is undermined and the free end folded under, creating a double layer of de-epithelialized tissue. The double-layered flap area is sutured subcutaneous to the contralateral buttock a few centimetres away from the midline, therefore creating two layers of tissue in the midline and transforming the natal cleft to a shallow groove. If the defect becomes larger than 10 cm a bilateral fasciocutaneous flap can be used. In our series we have treated 28 patients in this way and we have observed only two superficial wound infections and no recurrence after a follow-up period of between 3 months and 9 years (mean 4·5 years) The differences between the two methods are: (1) the lateral placed tension-free suture line is achieved by the V–Y-advancement procedure; (2) the natal cleft is filled with a double layer of tissue instead of one which is undermined and probably scarred from the wound edge; (3) no unaffected tissue is wasted. The results of Mr Kitchen show that the minor Karydakis flap is successful in the treatment of simple pilonidal disease. In complicated chronic recurrent disease, however, the more complex procedure of the V–Y-flap is justified The recurrent pilonidal sinus is an important surgical problem, the optimal treatment of which remains controversial.

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1 Schoeller Th, Wechselberger G, Otto A, Papp Ch. Definite surgical treatment of complicated recurrent pilonidal disease with a modified fasciocutaneous VY-advancement flap. *Surgery* (in press)

Author's reply

Sir

I appreciate the comments by Dr Schoeller and colleagues who confirm the two important requirements in preventing recurrence, i.e. flattening the deep intergluteal furrow and lateralizing the scar They suggest that a flap 1 cm thick will create an even deeper cleft, but this is not the case. The edge of the flap will be 1 cm thick as it is brought to the opposite side, but the depth at the midline will be much thicker owing to the bunching of tissue in the midline. This occurs as the depth of the undercut flap is brought across by deeply placed sutures which bring to the midline not only the base of the flap but also some of the subcutaneous tissue deep to it in the medial edge of the wound (*Figs 3* and *4*). The new midline sometimes appears as a series of shallow dimples produced by the insertion of the chromic catgut into the depths of the flap and is shallower than the original deep cleft. The cleft is not fully flattened as this would be cosmetically less acceptable, but it is shallow enough to prevent further collection of hairs. The wound itself may only be 1–1·5 cm lateral to the new midline but this is sufficient because recurrences always begin in the midline and are more likely if there is a portal of entry such as a wound The flap should not be so thin as to jeopardize blood supply and may sometimes need to be a little deeper than 1 cm in thickness. If it is wide enough (2 cm is usually enough) it can be advanced without tension and without wound edge necrosis

A simple V–Y flap is preferable to more complex rotation flaps and will flatten the furrow but usually end up with a midline scar[1], this may be susceptible to further hair entry although Dr Schoeller is recommending a double-layered de-epithelialized flap to lateralize the wound and create a shallow groove. I await with interest the publication of this method as it may be another way to lateralize the wound without tension It may be conceivable that a V–Y flap could be used as part of a Karydakis operation instead of undercutting the medial side of the flap and indeed this may be preferable where there is a lot of scar tissue or fibrosis but the upper and lower ends of this Y shaped scar will always cross the midline. Except in patients with bilateral openings it is best to avoid having any part of the wound in the midline. The beauty of the Karydakis method is its simplicity and effectiveness.

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1 Khatri VP, Espinosa MH, Amin AK. Management of recurrent pilonidal sinus by simple V–Y fasciocutaneous flap. *Dis Colon Rectum* 1994; 37: 1232–5.

British Journal of Surgery 1997, 84, 892–893

Book reviews

Anesthesia and Perioperative Care of the Combat Casualty. Textbook of Military Medicine. Part IV – Surgical Combat Casualty Care

R Zajtchuk, R. F. Bellamy and C. M. Grande (eds).
287 × 220 mm. Pp. 1931. Illustrated. 1995. Tacoma, Washington. TMM Publications. Price not supplied.

This large volume, comprising over 1930 pages, deals with anaesthetic and surgical techniques relevant to trauma for military and civilian practitioners. An interesting historical overview moves on to a vast archive built up over 150 years quoting multinational worldwide experience. Chapters are devoted to airway management, fluid resuscitation and physiological monitoring. Special reference is made to field deployment and mobile hospitals. Military anaesthetic machines, techniques and drugs are covered in detail and there are specific sections devoted to close circuit inhalation, intravenous anaesthesia and transfusion policy The illustrations are beautifully presented, the anatomical three-dimensional coloured prints which enhance the text about regional anaesthetics are outstanding, as are the plates of ballistic and burn wounds of many parts of the body. I recommend any surgical trainee to peruse these 170 pages, as important basic surgical principles are clearly demonstrated Metabolic derangements, nutritional support, multiple organ failure, ventilatory management and renal failure have chapters to themselves, and the various forms of military medical evacuation make for interesting reading. Problems such as hypothermia and chemical agents are discussed, giving insight into dealing with mass casualties in unpleasant conditions. Finally, there is a brief history of anaesthesia, from the time of Joseph Priestly to the present day. This volume is a welcome addition to trauma management. The authors have succeeded in crystallizing a vast field into an enjoyably readable form. I commend it to all those with an interest in the care of the injured.

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The Basic Science of Vascular Disease

A N. Sidawy, B. E. Sumpio and R. G DePalma (eds).
285 × 220 mm. Pp. 904. Illustrated. 1997. Armonk, New York: Futura Publishing Company. US$175.

Three distinguished editors have assembled an all-star cast from American academic vascular surgery to produce a wide-ranging, large textbook of basic science considerations in vascular practice. This text probably has no competitor at present, although one is forthcoming from Cambridge University Press. The book is divided into three sections. The first section covers the embryology, physiology and anatomy of the arterial venous and lymphatic system. Of special interest is the chapter on 'Molecular Biology and the Vascular Surgeon' by Peyman and Sumpio. Dr Sumpio is probably the best qualified surgeon scientist to write on this subject and the chapter bears his imprint. However, I think that to get through this chapter one needs to have a fairly advanced background in molecular biology, making it unsuitable for the beginner. The second section is entitled 'The Essential Tools for the Treatment of Vascular Disease' and comprises a slightly mixed bag, ranging from the function of endovascular devices and vascular grafts, to blood rheology and a discussion on lipoproteins in vascular disease. There is a chapter on statistics by Sushil Gupta which is very curious; it is essentially a simple primer of statistical techniques written by a surgeon and contains only a single example from the vascular literature. The third section is another mixed bag entitled 'The Science of Selected Titles' and, again, the subject matter ranges from a discussion of the genetics of aortic aneurysm formation to the mechanics of foot ulceration in diabetic neuropathy.

I feel that the editors have had a very difficult job in trying to range broadly over the whole spectrum of conditions that are met in vascular practice They have certainly not left any significant gaps but have had to sacrifice a certain amount of depth in return The chapters on vascular cell biology are very worthwhile and the many isolated chapters on miscellaneous topics are, for the most part, of good quality. These serve as a collection of essays to spark initial interest rather than as the support for any form of sustained study I recommend this book; it is the only one of its kind. It addresses the important biological issues in vascular disease In the UK, where the majority of vascular clinicians are still surgically trained, it is important not to lose sight of basic considerations in this disease I recommend this volume for every established vascular unit, particularly those that are involved in laboratory-based research

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Surgical Diseases of the Spleen

J. R. Hiatt, E. H. Phillips and L. Morgenstern (eds).
240 × 160 mm. Pp 285. Illustrated. 1997. Heidelberg: Springer. DM 198,00.

The spleen has always fascinated surgeons; many spleens were at one time removed for enjoyment rather than benefit. This delightful and readable book is an excellent summary of the history and practice of splenic surgery The chapters on trauma and on laparoscopic splenectomy are of particular value. The emphasis on splenic conservation is a recurrent and important theme, including good descriptions of partial splenectomy. Very full references make this a valuable source-book. The operation descriptions are fully detailed, as are possible complications Small bowel obstruction is listed among the latter; I would have added that this is always caused by a loop of jejunum becoming adherent to the splenic bed, and that this can usually be prevented by tucking the small bowel below the splenic flexure, firmly in the lower abdominal compartment, at the conclusion of the operation.

One surprising omission, in the section on postsplenectomy infections, is any mention of babesiosis This plasmodial infection is associated with a mortality of over 50 per cent and occurs almost exclusively after splenectomy. Death is often due to it being mistaken for malaria, out of ignorance. Although rare it is therefore very important. The commoner form in the USA is due to *B. microti* and is widespread but not yet reported from Southern California. The European infection with *B. divergens* is more serious, although only 22 cases have been reported I know of one unreported fatal case from the UK.

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Surgical Treatment of Anal Incontinence. 2nd ed.

C. V. Mann and R. E. Glass. 197 × 275 mm. Pp. 195. Illustrated. 1997. London: Springer. Price not supplied.

The first edition of this book was published 5 years ago and was a very readable and concise text on this slightly neglected aspect of coloproctology. As a relatively inexpensive book it filled a need admirably. The second edition, which includes recent developments, is bigger with more illustrations. New sections have been added, including those on general supportive measures and non-operative treatment in the management of incontinence, the use of laparoscopic techniques in rectal prolapse surgery, and newer developments in the use of the gracilis muscle for incontinence. As previously, the illustrations are of excellent quality and clarity. Along with the clearly written text they make the described surgical techniques easy to follow and understand. For this reason the book is indispensable as a 'cookery book' for the coloproctologist who is taking up incontinence surgery, giving clear guidelines on the pathology, investigations and assessment, and operative techniques available.

A. R. Berry

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Notices and announcements

6 June 1997
Clinical Practice and Changing Concepts in Carotid Surgery
Bristol, UK
Information P. Lamont, Surgical Directorate, Level 6, Bristol Royal Infirmary, Bristol BS2 8HW, UK

25–28 June 1997
CAR '97. Computer Assisted Radiology and Surgery
Berlin, Germany
Information: CAR '97, c/o Technische Universitat Berlin, Institut fur Technische Informatik, Sekretariat CG, FR 3-3, Franklinstrasse 28/29, D-10587, Germany

7–8 July 1997
Rectal Cancer Workshop
Singapore
Information. Y. H. Ho, Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 169608

13 July–22 August 1997
International Medical Students' Summer School
Manchester, UK
Information. Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

16–18 July 1997
British Association of Surgical Oncology 54th Scientific Meeting
Aberdeen, UK
Information. V. Hall, Administrator, BASO, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

26–27 July 1997
Hong Kong Surgical Forum – Summer 1997
Wanchai, Hong Kong
Information: Forum Secretary, Hong Kong Surgical Forum, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

31 August–3 September 1997
19th ESPEN Congress on Clinical Nutrition and Metabolism
Amsterdam, The Netherlands
Information. Van Namen and Westerlaken Congress Organisation Services, PO Box 1558, 6501 BN Nijmegen, The Netherlands

7–12 September 1997
8th International Congress on Cleft Palate and Related Craniofacial Anomalies
Singapore
Information: Dr L. Keuk, Organising Committee, Academy of Medicine, 16 College Road, Singapore 0316

12–17 October 1997
Management of Emergencies and Disasters: a Multidisciplinary Approach
Stoke, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

12–18 October 1997
Telemedicine and Telecare
Belfast, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

15–22 October 1997
Cancer in Children: Challenges and Controversies
London, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

23–24 October 1997
2nd Nottingham International Colorectal Cancer Symposium
Nottingham, UK
Information: J. D Hardcastle, Department of Surgery, University Hospital, Nottingham NG7 2UH, UK

7–21 November 1997
Hong Kong International Cancer Congress and Asian Pacific Cancer Congress 1997
Hong Kong
Information: Gloria Wong, Cancer Centre, Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

9–14 November 1997
Health Technology Assessment: the Pathway to Evidence-Based Practice – the UK Experience
Manchester, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

27–28 November 1997
31st Meeting of the Vascular Surgical Society of Great Britain and Ireland
London, UK
Information: T Szymanska, Vascular Surgical Society of Great Britain and Ireland, Countess of Chester Hospital, Liverpool Road, Chester CH2 1BQ, UK

25 February–1 March 1998
IX Asean Congress of Plastic Surgery
Penang, Malaysia
Information: M. Subramaniam, Department of Plastic Surgery, Hospital Ipoh, 30990 Ipoh, Perak, Malaysia

20–22 April 1998
The Paediatric Oesophagus. An Interdisciplinary Symposium. Main Topic: Gastro-Oesophageal Reflux with a Special Interest in Alkaline Reflux
Izmir, Turkey
Information. O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, 35100 Izmir, Turkey

13–15 May 1998
Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information: Association of Surgeons of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

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Following final approval of articles, authors are asked to submit the accepted version on disk. These should be IBM-compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, software, and disk system if known. **Do not justify.** Particular attention should be taken to ensure that any articles submitted adhere **exactly** to Journal style in all respects. Please send us digital versions of your figures. Ideally, these should be sent in native format or PICT if created on a Mac, or in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Avoid using tints if possible; if they are essential to the understanding of the figure, try to make them coarse Further details can be obtained from the publisher. Disks will not be returned to authors.

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Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts, which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; 296: 401–5 or the *Annals of Internal Medicine* 1988; 108 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

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Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a abstract of no more than 200 words on a separate page Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation. **Randomized controlled trials** should be clearly identified as such in the title and abstract.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J A Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no abstract is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 400 words (300 if accompanied by a figure), with no more than five references and one illustration

Surgical workshops

These describe technical innovations or modifications that may be useful in surgical practice These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4-cm margins. Manuscripts that do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page. title page, abstract, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction, methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed, (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

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The second page of the manuscript should carry an abstract of not more than 200 words. This should be broken into four paragraphs each with a clear heading as follows. *Background* this should state why the study was done, and its main aim; *Method* this should describe patients, laboratory material and other methods used; *Results* the main findings of the study should be stated briefly, including important numerical values; *Conclusion* the main conclusion drawn from the Results should be stated. Controversial or unexpected observations may be highlighted, but this section should be brief. The summary should identify clearly the nature of the study· randomized controlled trial, retrospective review, experimental study, etc. It should be written in clear prose.

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Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. Line drawings are acceptable as clear black on white graphics, computer printout or photocopies. Radiographs, photomicrographs, etc should be submitted in the form of glossy prints, original transparencies or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout If a table or an illustration has been reproduced from a published work the original source must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension by the reader. Abbreviations should be used consistently throughout the text and must be clearly defined on first use

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg) Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above. Uniform Requirements for Manuscripts Submitted to Biomedical Journals) Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, references should be numbered consecutively by superscript: ^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be· author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number; page numbers. For example· De Bolla AR, Obeid ML. Mortality in acute pancreatitis *Ann R Coll Surg Engl* 1984, **66.** 184–6. The sequence for the chapters of a book should be· author(s); chapter title; editors; book title; place of publication, publisher, year of publication; page numbers For example· Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures In Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer, 1981. 123–63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *Br J Surg* 1991; **78.** 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of data, the *analysis* of data and the *interpretation* of results.

Design

Authors should set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study The use of standard deviation and standard error should be clearly distinguished. Use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant' Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data

British Journal of Surgery 1997, 84, 897–898

Leading articles

Minimal dissemination of solid epithelial tumours: impact on staging and therapeutic strategy

Despite radical surgical procedures employing extended lymphadenectomy, metastatic relapse remains a frequent event in patients with solid tumours. A major reason for this disturbing problem is that small occult quantities of tumour cells may disseminate early in the course of the disease. Failure to recognize these cells may eventually lead to failure of local treatment. To obtain a more refined tumour staging system it is, therefore, important to develop sensitive assays that allow the detection of individual disseminated tumour cells. As recent studies demonstrate, the detection of single isolated epithelial tumour cells in mesenchymal secondary organs (e.g. bone marrow, lymph nodes) or the peritoneal cavity is possible using new sensitive immunohistochemical assays; these assays employ monoclonal antibodies directed against epithelial or tumour-associated marker proteins[1–8]. At present, antibodies to cytokeratins as major constituents of the epithelial cytoskeleton are regarded as the most specific and sensitive probes for detecting isolated epithelial tumour cells in bone marrow or lymph nodes. The incidence of individual tumour cells in bone marrow aspirates, obtained at primary surgery for gastrointestinal cancer, oesophageal cancer and non-small-cell lung cancer, varies from 32 to 60 per cent[4,7,8], and the detection of these cells indicates an unfavourable prognosis. In the case of lung cancer, there is no evidence that surgical resection of the primary tumour induces blood-borne tumour cell dissemination into the bone marrow.

Applying immunohistochemistry to the reanalysis of lymph nodes classified as 'tumour free' by routine histopathological examination reveals considerable rates of early lymphatic dissemination in patients with resectable primary tumours: non-small-cell lung cancer 15 per cent, gastric cancer 25 per cent, pancreatic head cancer 43 per cent and oesophageal cancer 62 per cent[2,3,5,6]. The presence of these tumour cells is an independent prognostic factor in terms of relapse-free survival. In lung cancer, there is no correlation between the presence of micrometastatic cancer cells in lymph nodes and bone marrow, suggesting that haematogenous and lymphatic tumour cell spread are governed by different mechanisms.

In the near future, immunocytochemical assays should become acceptable for international tumour staging classifications. Further improvements in existing assays, such as automated analysis of large numbers of cells and enrichment of tumour cells with immunomagnetic beads, may help to overcome the problem of low tumour cell concentration. To develop a standardized procedure that may then serve as a gold standard for other diagnostic approaches, several groups have developed reverse transcriptase–polymerase chain reaction assays that screen for epithelial-specific or tumour-associated messenger RNA (mRNA) species in samples from bone marrow, lymph nodes and blood[9]. The specificity of this approach might not be absolute, but rather reflect quantitative differences in the expression level of malignant cells and the surrounding autochthonous cells. Thus, illegitimate ectopic expression of small amounts of epithelial mRNA in mesenchymal cells might also be detected if the amplification of the transcribed complementary DNA is extensive, which can result in false-positive results[10]. It is worthy of note that almost all of the information on the prognostic relevance of early disseminated tumour cells stems from immunocytochemical analyses. Therefore the clinical significance of new molecular methods of detection, based on the application of the ultrasensitive polymerase chain reaction, needs to be demonstrated in large prospective studies.

The biological significance of micrometastatic tumour cells remains poorly understood. Immunocytochemical double staining analyses and cell culture studies have demonstrated that the potential of these cells to form overt metastases is still variable[11,12]. In diseases such as colorectal cancer the situation is particularly disturbing, as the frequent occurrence of single tumour cells in bone marrow is a strong and independent predictor for metastatic relapse in other organs, while the manifestation of skeletal metastasis is rare[7]. It seems, therefore, that only a fraction of these cells represents the seed of subsequent metastases arising in the skeleton, while the majority of them appear to leave the bone marrow and settle in another secondary organ where a better environment for outgrowth exists. The extended latency period, between the detection of micrometastatic cells at the time of primary surgery and overt metastatic relapse, suggests that these cells may not initially have the potential to form detectable metastases. This 'dormant' state of micrometastatic cells is supported by the observation that only a small number of the cells react with monoclonal antibodies to nuclear proliferation-associated proteins, such as Ki-67 and p120[11]. This observation leads to the consideration that micrometastatic tumour cells might not be suitable targets for adjuvant therapy with antiproliferative chemotherapeutic agents. For the minimal residual tumour load in patients with micrometastatic tumour cells, new therapeutic strategies with less severe side-effects, such as intravenous application of monoclonal antibodies against tumour-associated cell surface antigens, might be an alternative or an adjunct to systemic chemotherapy[13].

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The E-cadherin-mediated cell–cell adhesion system in human cancers

The process of cancer invasion and metastasis comprises a complex series of sequential steps. The initial step is the dissociation of cancer cells from the primary tumour through the breakdown of the cell adhesion system which includes integrins, selectins, CD44 and the cadherin families of molecules. Cadherins, which are a family of transmembranous glycoproteins responsible for calcium-dependent intercellular adhesion, bind cells tightly by homophilic interaction in the presence of calcium ions; the inactivation of other adhesion systems has little effect on cell–cell adhesion when cadherins are functioning normally[1,2].

E-cadherin, one of the classical cadherins, plays an important role in epithelial integrity. It has been shown by immunohistochemical techniques to be expressed on the cell–cell boundaries of non-cancerous epithelial cells without exception[3]. On the other hand, E-cadherin is frequently reduced or absent in cancer cells, which suggests that an impaired E-cadherin-mediated cell–cell adhesion system is a characteristic of cells with malignant transformation.

Previous studies, using immunohistochemical staining and Western blotting, have demonstrated that reduced E-cadherin expression is associated with tumour dedifferentiation, increased invasiveness and a high incidence of lymph node metastasis in a number of human carcinomas. Patients with normal expression of E-cadherin have a better prognosis than those with reduced expression in studies of carcinoma of the head and neck, stomach, bladder, prostate and oesophagus[4]. These observations are supported by *in vitro* studies, which have evaluated the influence of E-cadherin function on cell behaviour and suggest a possible role of E-cadherin as an invasion suppressor molecule[1,5].

Linkage between cadherins and the actin filaments of the cytoskeleton is necessary to form strong cell–cell adhesion. This linkage is localized at the adherens junction and is mediated by many associated junctional undercoat proteins, including catenins, vinculin and actin. Catenins are a group of proteins which interact with the intercellular domain of E-cadherin and comprise α-(102 kDa), β-(88 kDa) and γ-(82 kDa)catenin[6]. The α-catenin gene is located on chromosome 5q21–22 and the β-catenin gene on 3p21.

Many previous reports have suggested that decreased adhesive function of E-cadherin may occur in a number of ways including: (1) downregulation of E-cadherin expression; (2) abnormal catenins, including deletion or mutation in the genes that encode them; and (3) biochemical modification of catenins, for instance the phosphorylation of β-catenin.

The loss or reduction of E-cadherin expression is now considered to be due to mutation in the E-cadherin structural gene, to suppression or impairment of transcription of the E-cadherin gene, or to protease cleavage of cadherin peptides. Allelic loss of the E-cadherin gene locus 16q22·1 has been reported in 30–50 per cent of breast, prostate and hepatocellular carcinomas. Although mutations within the E-cadherin coding sequence in breast, gastric and gynaecological cancers have been reported as rare, mutated cadherin molecules whose catenin-binding sites in the cytoplasmic domain are deleted cannot bind to the cytoskeleton and concomitantly lose their cell binding function, according to a report by Nagafuchi and Takeichi[7].

With regard to suppression of transcription of the E-cadherin gene, it has been shown that reduced E-cadherin messenger RNA (mRNA) levels are associated with increased mRNA levels of $\beta 1$ and $\alpha 5$ integrins and fibronectins in prostatic tumours, or with overexpression of erb-B_2 receptor in human mammary epithelial cells. Additionally, in human breast and prostate carcinomas, the frequent loss of E-cadherin expression has been reported to result from hypermethylation of 5′ CpG islands within proximal promoter regions of the E-cadherin gene[8].

A mechanical linkage between E-cadherin and the cytoskeleton through catenins is critical for E-cadherin to function normally. Deletion of the α-catenin gene or mutation of the α-catenin protein, as demonstrated in the human lung cell line PC9 by Shimoyama *et al.*[9], and mutation of β-catenin as described in the gastric cancer cell line HSC-39 (which expresses normal E-cadherin and α- and γ-catenin, but mutated β-catenin) results in non-aggregating and non-compacting cells. However, no evidence for mutations in the α- and β-catenin genes has been reported in human gastric and breast carcinomas[10].

It has also been shown that certain motility factors, including hepatocyte growth factor and epidermal growth factor[11], induce tyrosine phosphorylation of β-catenin. This results in the redistribution of E-cadherin from the intercellular junction to other areas which leads to increased cell dissociation, motility and invasion. In addition, recent studies demonstrate that α-catenin and β-catenin associate with the adenomatous polyposis coli (APC) protein. It has also now been confirmed that the APC protein forms distinct heteromeric complexes, containing a combination of α-catenin, β-catenin and plakoglobin, which are independent of the cadherin–catenin complexes; β-catenin and plakoglobin are central regulators of cell adhesion, cytoskeletal interaction and tumour suppression[12].

Overall, numerous studies have suggested that E-cadherin and its cytoplasmic undercoat proteins, including α- and β-catenin, are molecules that suppress tumour invasion and metastasis. There is a strong inverse relationship between decreased or aberrant expression of these molecules and poor prognosis in patients with cancer. However, the function of the cadherin–catenin complex is involved to a more profound extent in cancer cell biology. Further studies of the cadherin-mediated cell–cell adhesion system may allow us to elucidate a means of regulating or restoring function to this system in pathological states. This may provide a basis for the treatment of patients with cancer.

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Editorial

The referee process of *The British Journal of Surgery*

The British Journal of Surgery recently took part in an international survey concerning review methods used by journal editors in determining the validity of submitted manuscripts, and contributed to the 119 questionnaires (73 per cent compliance) that were returned. The following conclusions were made: (1) editors rate criteria such as 'valid data' and 'scientific merit', which emphasize the validity of research, highly in accepting or rejecting manuscripts; (2) editors employ criteria such as 'expertise in a subject area' and 'prior research experience' as most important in the selection of editorial boards and manuscript reviewers; (3) samples of editors' resubmission requirements addressed important methodological criteria such as study design in only 33 per cent of papers, statistics in 42 per cent and measurement assessment in 7 per cent (W. C. Steinmann, personal communication, 1996).

A recent study showed that authors could not identify or guess the identity of reviewers of their papers, whether rejected or accepted. For the specialist journal concerned (*Psychological Medicine*), most referees remained anonymous[1]. Few studies have examined the effect of peer review and editing on the quality of articles subsequently published. Pierie *et al.*[2] recently showed that peer review in *Nederlands Tijdschrift voor Geneeskunde* (*Dutch Journal of Medicine*) significantly improved question scores and general medical value. Editing led to further significant improvements in style and readability. No differences were found between the scores of four categories of evaluator.

Referees, submitted articles, published articles and subscriptions

The Journal currently has over 1200 referees, of whom 960 (80 per cent) are based in the UK, 82 (7 per cent) in the USA, 80 (7 per cent) from the rest of Europe and about 8 per cent from the rest of the world. The composition of the Editorial Board is shown in *Table 1*. Some referees work exceedingly hard for the Journal; during 1995, for example, 14 made criticism of 15 or more submitted articles each. Editors rapidly appraise referee performance in a subjective way. Subjective features include evidence that the referee has actually read the article, an incisive critique that might make criticism not only of the novelty of the work, but also of methodology and analysis. Very good referees pick up errors in syntax, grammar and even inappropriate or inaccurate references. *The British Journal of Surgery* keeps a blacklist of referees but this is determined, for the moment, on tardy returns and the number of reminder letters that are required to prompt referee activity. The editors welcome comments from referees on the maximum number of papers they are able to handle efficiently each year.

The number of articles submitted to the Journal has a tendency to rise slowly: 1257 in 1991, 1357 in 1992, 1400 in 1993, 1443 in 1994, 1498 in 1995 and 1467 in 1996. By and large, the origin of submissions and subscriptions is similar. *Table 2* shows the submissions and subscriptions data for 1993, and the specialty interest of the articles published in the Journal for 1995 is shown in *Table 3*. The publication dynamics in 1993 and 1995 are shown in *Table 4*. The average time taken by authors to make a resubmission following a request for amendment or corrections is 80 days. Not all delays in publication, therefore, relate to Journal dynamics. It is hoped that the editors can reduce the 'time to publication' from its current 6·5 months.

In 1995 only 18 per cent of submissions were rejected without referee criticism; these were nearly all case reports. Less than 0·5 per cent of papers were accepted without review, and these were Leading Articles. The mean referee turnaround time in 1995 was 25 days, and in that year the overall rejection rate was 979 (65 per cent) of 1498 papers.

Table 1 Composition of the Editorial Board

Country of origin	No.
Russia	1 (2)
Middle East	2 (3)
Africa	3 (5)
Australia or New Zealand	3 (5)
South America	5 (8)
Far East	7 (11)
USA and Canada	8 (12)
Rest of Europe	17 (26)
UK	20 (30)

Values in parentheses are percentages

Table 2 Submission and subscription data for 1993

	Percentage of 1400 submissions	Percentage of 8000 subscriptions
UK	45	36
Europe (excluding UK)	31	23
North America	4	18
Japan	5	4
Rest of the World	15	19

Table 3 Specialty interest of articles published in the Journal during 1995

Specialty interest	No. of articles ($n = 425$)
Lower gastrointestinal tract	106 (25)
Hepatic–pancreatic–biliary	102 (24)
Upper gastrointestinal tract	61 (14)
General	61 (14)
Vascular	51 (12)
Breast or endocrine	29 (7)
Trauma	15 (4)

Values in parentheses are percentages

Table 4 Publication dynamics in 1993 and 1995

Article	1993	1995
Submission to rejection	55 days	53 days
Submission to acceptance	144 days	137 days
Acceptance to publication	6·7 months	6·5 months

Referee performance

Each paper is generally refereed by two people, and concordance between referees was examined in a sequential sample of 190 papers. *Table 5* shows the degree of concordance between referees (labelled A and B) where the four possible categories of recommendation given by the referee are plotted one against the other. Referees make any of the following four recommendations: 'accept without modification', 'accept with minor changes', 'major changes required – possibly accept' and 'reject'. *Table 5* shows that there is complete accord between referees in 38 per cent of articles, broad agreement in 41 per cent, discord in 17 per cent and complete disagreement in only 3 per cent. For the 76 papers where there was discord and/or complete discord of view, one editor (J.R.F.) sided with the more critical referee on 61 occasions (80 per cent). When discord does occur, a third referee is asked to arbitrate or act as 'hanging judge'.

Each referee is asked to score each article on four features: (1) originality; (2) clinical and scientific importance; (3) clarity of presentation, grammar and style; and (4) analysis of data and statistical methods. Studying the same 190 papers with reports from two referees, each feature was awarded a score of one point for 'poor', two points for a 'moderate' standard, three points for 'good' and four points for 'excellent'. It is acknowledged that each of the features may not be worthy of similar point allocations, but the purpose of the analysis was to detect any major point discord that correlated with the final opinion of each referee. Papers recommended for 'accept without modification' achieved a mean score of 11·8; concordant 'accept with minor change' achieved a mean score of 12·0. Papers recommended for 'major changes required' had a mean score of 9·7 and those for

Table 5 Concordance of referees in 190 papers

	Referee A			
Referee B	Accept	Minor changes	Major changes	Reject
Accept	3	13	15	6
Minor changes		31	40	17
Major changes			19	24
Reject				22

'reject' achieved a mean score of 8·5. Papers with major discord, that is those labelled 'accept with minor changes' by one referee which the other referee had labelled 'major changes required' or 'reject', scored means of 13·0 and 8·5 respectively. It is obvious that referees score papers to an appropriate level, whether they reject or accept, and mark consistently within the accepted bands, even when there is a discordant referee view.

Outcome of the referee process

This quality assurance study did not examine the beneficial or detrimental effects of the current referee process. An area of concern is the fate of rejected papers. If many high-quality papers were rejected inappropriately, it should be possible to trace them in other journals, although it must be acknowledged that the referee process may have improved these articles so much that their acceptance by other journals was assured.

Fifty rejected papers from 1991 were selected at random. The time gap of 5 or 6 years was chosen to ensure a substantial opportunity for authors to publish elsewhere. Attempts were made to trace the rejected articles by author and title in various medical publication indices. Thirty-four of the 50 rejected papers were not traced. The 16 papers that had been published were found in *Diseases of the Colon and Rectum* (two), *Transplantation* (one), *Surgical Oncology* (two), *Australian and New Zealand Journal of Surgery* (two), and other European (five) and international (four) journals.

Conclusions

1 The referee process of the Journal appears reasonably robust.
2 The process seems to work across a wide range of specialty interest.
3 Potentially worrisome discord occurs in 40 per cent of paired referees.
4 The discord is usually due to lack of incision by one referee (80 per cent).
5 Only a few articles are lost to other 'significant' journals.

For the future

A further prospective study is under way which will compare the concordance between referees chosen by the editors and by authors. It is hoped that this will cast further light on the referee mechanisms of *The British Journal of Surgery* and so allow an improvement in the quality of the editorial process and eventually in the Journal itself.

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1 Wessdy S, Brugha T, Cowen P, Smith L, Paykel E. Do authors know who refereed their paper? A questionnaire survey *BMJ* 1996; 313: 1185.
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Review

Functional problems in adult rectal prolapse and controversies in surgical treatment

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Background Rectal prolapse is a condition that has fascinated surgeons for a long time. To date, no single ideal surgical treatment has been identified. The aetiology of rectal prolapse remains highly controversial, but it is recognized that associated functional problems, such as incontinence and constipation, are common. The pathophysiology, and controversies surrounding continence and constipation, remain topics of debate.

Method All relevant papers derived from Medline and manual searching on rectal prolapse and associated functional problems were reviewed.

Results and Conclusion The surgical management of rectal prolapse has evolved from historical encirclement procedures to current minimally invasive ones. Successful management must include adequate attention to the associated functional problems in order to eradicate the basic abnormality.

Rectal prolapse or procidentia is a disabling problem and controversies regarding its management continue to stimulate interest in the study of its aetiology, pathophysiology, functional aspects and concepts of surgical management. It was Hippocrates who first described the procedure of shaking the patient while hanging by the heels to reduce the prolapse.

Many surgical techniques for rectal prolapse were described during the last century; none has been shown to be ideal. The procedure chosen is usually based on the fitness of the patient and the surgeon's familiarity and preference for a particular surgical approach. The functional aspects of rectal prolapse should also be considered in order to treat a patient with rectal prolapse optimally.

Historical background and pathophysiology

The pathophysiology of rectal prolapse was first described in the late 19th century, long before abdominal surgery was considered safe[1–4]. The early operations described for the condition were perineal procedures, one of which is the Mikulicz procedure (a perineal rectosigmoidectomy) first performed in 1889[1]. However, the aetiopathology of rectal prolapse remained unknown until 1912 when Moschcowitz[5] proposed the theory of a sliding hernia through a defect in the pelvic fascia as a cause of rectal prolapse. His theory was based on the presence of a deep rectovescial or rectovaginal pouch in most patients with a complete procidentia. He then went on to describe the Moschcowitz procedure which involved the obliteration of the peritoneal pouch of Douglas by a purse-string. The recurrence rate was, however, 80 per cent.

Broden and Snellman[6] in 1968 discounted Moschcowitz's theory and put forward the concept of a circumferential intestinal intussusception; the authors demonstrated this phenomenon through cine-radiography. Porter[7] in 1962 reported that reflex inhibition of the external sphincter and levator muscles by distension of the rectum was more profound and prolonged in patients with rectal prolapse. Parks *et al.*[8] in 1977 showed that mean resting pressures were decreased while maximum squeeze pressures were maintained in those with rectal prolapse, suggesting a dysfunction of the internal sphincter as a cause of the prolapse. Neill *et al.*[9] reported findings similar to those of Parks when they demonstrated a decrease in the mean resting pressure but a normal maximum squeeze in continent but prolapsing patients. It is, however, difficult to prove if any or all of the above features are the cause or the effect of rectal prolapse.

There are many other conditions found in association with rectal prolapse. One such association is a connective tissue disorder. Marshman *et al.*[10] in 1987 reported that many patients had an associated increased joint mobility. Other associated factors in rectal prolapse include mental illness[11], neurological disorders[12] and parity[12]. Corman[13] described nulliparous women as having the greatest risk of developing rectal prolapse.

Some authors have attributed the pathogenesis to an imbalance of forces between the striated muscles of the abdominal wall and the pelvic floor. The levator ani muscles of the pelvic floor act in conjunction with the anterior abdominal wall muscles in supporting the pelvis and abdominal contents, and maintain a normal intra-abdominal pressure. It is, therefore, reasonable to suppose that an increase in pressure from above in conjunction with a deficiency or weakness of the pelvic floor musculature will cause some form of a prolapse or descent to occur[14–17]. This theory has been adopted widely by the gynaecologists and may explain a spectrum of conditions, ranging from a small rectocele, cystocele or vault prolapse to complete rectal prolapse[14,18–20]. Some authors have reported that rectal prolapse is associated with genital prolapse in up to 50 per cent of cases[21].

Closely associated with rectal prolapse, although a rather uncommon entity on its own, is solitary rectal ulcer syndrome (SRUS). Tjandra *et al.*[22] reported a series of 80

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patients with SRUS; 15 per cent had associated rectal prolapse and another 12 per cent had associated mucosal prolapse. Other authors[23–26] have reported that up to 80 per cent of patients with SRUS have either overt or occult rectal prolapse. It is, however, difficult to determine if one is the cause of the other as SRUS can occur without overt or occult rectal prolapse and vice versa. Furthermore, internal or occult prolapses can be found in a high proportion of healthy asymptomatic individuals who have undergone defaecography[26]. Nevertheless, there is a definite relationship between these two pathological conditions and many studies have shown that treating the rectal prolapse often heals the ulcer as well[22,23].

Functional problems in rectal prolapse

Continence

There is considerable controversy about the cause of rectal prolapse-associated incontinence. Many demonstrable changes associated with incontinence and rectal prolapse serve only to suggest that the two are closely related, but it is not possible to show if one is the cause or the outcome of the other. Keighley and Shouler[27] demonstrated an increase in sigmoid motility in incontinent patients with prolapse, while continent patients had normal sigmoid motility but a delayed whole gut transit. The authors therefore suggested an increase in bowel motility as a cause of prolapse-associated incontinence.

Matheson and Keighley[28] found a significantly decreased resting and squeeze anal pressure in incontinent patients with prolapse, but normal pressures in continent patients. Neill *et al.*[9], however, showed that resting pressures were also decreased in those with rectal prolapse who were continent. Gordon found evidence of denervation of puborectalis and external sphincter muscles in incontinent patients[29]. Continent patients, on the other hand, do not have electromyographic or manometric evidence of denervation, suggesting that denervation is probably a manifestation of rectal prolapse and not its cause[29].

The fact that the internal anal sphincter plays an important role in continence in rectal prolapse is shown by the significant improvement in internal anal sphincter electromyographic frequency and mean resting pressure after successful continence-correcting surgery[30–34]. Although the internal anal sphincter seems to improve after surgery, its pressures are still significantly lower than those found in normal controls[30,31]. Farouk *et al.*[31] suggested that repair of rectal prolapse probably allows the internal anal sphincter to recover by removing the cause of persistent rectoanal inhibition. Other authors[25–37] have shown that both the mean resting pressure and maximum squeeze pressure increased after successfully treating prolapse-associated incontinence, suggesting that the external sphincter component may also have a role to play in continence.

Duthie and Bartolo[38] claimed recently that the recovery of continence after operation does not depend on sphincter recovery but on improved anorectal sensation. Delemarre *et al.*[36] found an increase in rectal compliance and capacity after surgery in patients treated successfully for rectal prolapse and incontinence. Some surgeons have come up with a predictive score of continence after operation. The factors assessed included a delayed leakage during a saline infusion test, a narrow anorectal angle during pelvic floor contraction, minimal pelvic floor descent during contraction, and a long anal canal at rest and during pelvic floor contraction[39].

The recovery of continence after rectal prolapse surgery has also been reported to be related to the surgical procedure performed. Abdominal procedures seem to yield better results than perineal procedures. Perineal operations usually provide a 45–60 per cent chance of improvement in continence while abdominal procedures generally result in a 60–90 per cent chance[40–47]. Although the exact determinants of postoperative recovery of continence remain debatable, it is known that patients with extremely low anal pressures before operation are less likely to improve after surgery, regardless of the operative procedure chosen[34,37].

Constipation

The association of constipation with rectal prolapse has been reported to vary from 25 to 50 per cent[48,49]. The exact cause of constipation is, again, controversial and poorly understood. Metcalf and Loening-Baucke[49] demonstrated a paradoxical increase in external anal sphincter electromyographic activity in those with rectal prolapse who were constipated. Some authors, however, have attributed constipation to a delay in colonic transit[9,50].

There is also much debate about the cause of constipation following rectal prolapse surgery. Abdominal rectopexy without colonic resection or sigmoidectomy was found to give a significantly higher incidence of constipation[34,40,43,48,51,52]. McKee *et al.*[51] found an increase in compliance of the sigmoid colon, secondary to a redundant sigmoid loop causing hold up and kinking at the rectosigmoid junction, as a cause of constipation following rectopexy without sigmoidectomy. Allen-Mersh *et al*[53] demonstrated an increase in rectal wall thickness following rectopexy and claimed that this increase in thickness impedes the passage of stool into the lower rectum causing constipation. They also found that the increase in rectal wall thickness was related to rectal mobilization and not to any foreign material used in rectopexy.

Speakman *et al.*[54] recently showed in a prospective randomized trial that division of the lateral ligaments during rectopexy caused constipation, although it prevented the recurrence of rectal prolapse. The authors found no recurrence of prolapse in patients in whom the lateral ligaments were divided, and a recurrence rate of 50 per cent in those in whom the lateral ligaments were not divided. The mean anal canal pressures and rectal sensory threshold increased significantly in patients with divided lateral ligaments, suggesting neuropathy as a cause of constipation after surgery.

However, some surgeons have found no increase in postoperative constipation after rectal prolapse surgery, regardless of the procedure chosen[33]. Most operators routinely divide the lateral ligaments when performing a rectopexy and so, if neuropathy is a cause of constipation, one should expect to find more patients with constipation after rectopexy; this is not, however, the case.

Generally, most surgeons perform a sigmoidectomy for patients who are severely constipated before operation[48,55–58]. A subtotal colectomy has also been found to be helpful in patients with an associated delay in colonic transit demonstrated before operation[48,49].

Options for surgical treatment

The management of rectal prolapse is usually surgical. However, the options are many, indicating that doubt still exists regarding the ideal choice. Surgical approaches for rectal prolapse can be classified into either transabdominal or perineal (*Tables 1* and *2*).

Perineal procedures were first used in the late 19th century as abdominal surgery was then considered unsafe[1–4]. Moschcowitz first described the obliteration of the peritoneal pouch of Douglas based on the fact that rectal prolapse is commonly associated with an abnormally deep cul-de-sac[5,59]. However, recurrence rates as high as 80 per cent have been reported.

Anal encirclement was first described in 1891 by Thiersch[4]. Advantages of this procedure included simplicity, repeatability and that it required only a local anaesthetic. However, anal encirclement does not cure the disease process; it merely prevents rectal descent, leaving the patient symptomatic[60]. Although silver wire was the original material described by Thiersch, newer materials are now used, including silicone rubber impregnated with Dacron (Du Pont, Wilmington, Delaware, USA)[61,62], silicone rubber suture[63], knitted Dacron vascular grafts[64], silicone rubber rods[65] and the Angelchik antireflux prosthesis (Heyer-Schulte Corporation, Goleta, California, USA)[66]. Silver wires have been found to be prone to breakage, wire erosion, infection and skin sloughing[54]. There is a trend towards placing the encircling material higher in the ischiorectal fossa to prevent erosion and sloughing problems[50]. Sainio *et al.*[67] reported the use of high anal encirclement with polypropylene mesh in the treatment of rectal prolapse, with a recurrence rate of prolapse of 15 per cent. There was also a high rate of faecal impaction after surgery. In view of the generally high recurrence rate associated with anal encirclement, ranging from 20 to 60 per cent[63–65,68–70], and the high risk of faecal impaction, this procedure is now reserved only for patients who are debilitated and of high anaesthetic risk.

Table 1 Results of various abdominal procedures for rectal prolapse

Procedure	No of patients	Recurrence (%)
Ripstein rectopexy[40,42,57,91–93,96–98,107,132,133]	64 (22–500)	5 (0–13)
Wells rectopexy[39,102–105,134]	40 (30–135)	6 (2–10)
Suture rectopexy[108,110–113,135,136]	42 (18–257)	3 (0–5)
Resection rectopexy[48,57,115,140]	102 (47–125)	2 (0–6)
Anterior resection[41,56,139]	41 (28–113)	7 (4–9)

Values are median (range)

Table 2 Results of various perineal procedures for rectal prolapse

Procedure	No. of patients	Recurrence (%)
Anal encirclement[35,62–65,68–70]	18 (9–52)	29 (0–60)
Delorme operation[44,84–89,137,138]	22 (12–44)	10 (5–21)
Perineal rectosigmoidectomy[45,47,71,73,74,76–81]	25 (9–131)	6 (0–44)

Values are median (range)

Mikulicz[1] first described perineal rectosigmoidectomy in 1889 and the procedure was repopularized in the 1960s by Altemeier and colleagues[71]. This procedure is based on fixing the bowel to the sacrum by fibrosis around the anastomosis while at the same treating the constipation and preventing volvulus[72,73]. This form of treatment is now quite commonly used in some centres, although recurrence rates ranging from 0 to 50 per cent have been reported[7,37,45,47,71,74–81]. Johansen *et al.*[75] found the procedure of perineal rectosigmoidectomy to be safe and effective in the elderly, with no early recurrence. Ninety per cent of their patients were also found to have an improvement in continence following surgery, even when there was a demonstrable neuropathy before surgery. The authors concluded that pudendal nerve terminal motor latency is not an accurate predictor of postoperative continence[75]. Williams *et al.*[45] showed that inclusion of a levatoplasty procedure in patients undergoing rectosigmoidectomy significantly improves continence after operation.

The Delorme operation is a modification of perineal rectosigmoidectomy in which the prolapsed bowel is not resected; its mucosa is stripped and the muscularis propria of the rectum and sigmoid are plicated and replaced above the levator muscles[82]. Recurrence rates ranging from 5 to 21 per cent have been reported[44,83–89]. This procedure, while quite commonly performed in the UK in elderly and unfit patients, is rarely used in the USA.

Abdominal procedures for rectal prolapse usually involve rectal fixation, large bowel resection or a combination of the two. Rectal fixation, or rectopexy, which was first described by Pemberton and Stalker[90], involves full rectal mobilization followed by fixation of the rectum to the sacrum. Most surgeons use a foreign material to help anchor the rectum to the sacrum.

The Ripstein procedure is one of the most commonly used rectal fixation operations. It involves completely wrapping the mobilized rectum with a foreign material and suturing it to the sacrum[91–93]. The possible complications include erosion of the foreign material and fistula formation[94–98], and radiological and endoscopic stenosis[99–101]; it gives similar results to the Wells procedure[39,100–104]. The presence of a foreign material has been shown to be associated with an increased risk of pelvic sepsis and is therefore, potentially, dangerous[105]. However, if the use of a foreign material is inevitable, Marlex (C. R. Bard, Billerica, Massachusetts, USA) or polytetrafluoroethylene are advised since they become infected less commonly[106,107]. Some authors[108,109] have reported that a foreign material is not important in the provocation of an intense fibrous tissue formation, and have shown that sutures alone are sufficient and allow equally low recurrence rates of 0–4 per cent[108,110–113]. Duthie and Bartolo[33] have reported that patients with suture rectopexy not only have comparable postoperative manometric readings to those in whom foreign material is used, but also have significantly improved continence, when compared with a group with prosthetic material.

Anterior resection has also been described in the treatment of rectal prolapse. The principle in this case is the creation of fibrosis between the anastomosis and the sacrum[55,56]. Resection of the sigmoid colon also results in straightening and a decrease in the mobility of the left colon, and hence a reduced chance of torsion and volvulus[114,115]. The other advantages of anterior resection include the absence of foreign material and that it is a relatively simple surgical procedure[55,114]. Recurrence rates of prolapse following anterior resection have been reported to be fairly low[41,55,56]. A major disadvantage of this procedure, however, includes a possible decrease in continence secondary to a decrease in rectal reservoir[48]. The problems associated with the anastomosis are also well known. For patients with documented slow transit constipation and no pelvic outlet obstruction, subtotal colectomy has been recommended by some surgeons, with good result[48].

A combined colonic resection and rectopexy is also commonly performed. This makes use of the advantages of resection and avoids the disadvantages of rectopexy alone, especially with regard to constipation[94]. Recurrence rates for resection rectopexy range from 2 to 8 per cent[48,57,114,115]. Generally, resection rectopexy is reserved for patients who have a history of severe constipation.

Special issues in the surgical management of rectal prolapse

Rectal prolapse with solitary rectal ulcer syndrome

Reports have shown that up to 80 per cent of patients with SRUS have an associated rectal prolapse[23–26]. Tjandra *et al.*[40] looked at a group of 169 patients with rectal prolapse and found that 12 per cent of them had an associated SRUS. There is, therefore, a close association between the two conditions. The management of rectal prolapse with SRUS is, however, still highly controversial.

Generally, if the patient has symptomatic SRUS but an asymptomatic or occult prolapse, a trial of medical treatment should be commenced. This consists of an adequate fibre intake, defaecation training (especially against straining) and a judicious use of laxatives and enemas to facilitate evacuation. Both van den Brandt-Gradel's and Keighley's groups have documented good success rates using this regimen[116,117]. However, if such treatment fails, surgery may be advised. Many of the surgical procedures already described for rectal prolapse have been used, with success in ulcer healing of 25–100 per cent[40,118,119]. Patients with full-thickness rectal prolapse and SRUS tend to do better than those with occult prolapse[30,118,119].

If a patient has a symptomatic rectal prolapse but asymptomatic SRUS, surgery should be advised as for rectal prolapse alone. However, the ulcer will heal in only about a third of these patients despite successful correction of the prolapse[40].

One can conclude from these data that patients with symptomatic SRUS but an asymptomatic rectal prolapse tend to do better in terms of healing of the ulcer than patients who have an overt rectal prolapse but an otherwise asymptomatic SRUS. This may be of little clinical importance as the latter group is asymptomatic anyway in terms of the associated rectal ulcer.

Rectal prolapse with associated rectocele, cystocele or vault prolapse

Often, rectal prolapse is associated with a small mid-level rectocele or cystocele. However, it is uncommon for rectal prolapse to be found in association with gross uterine or vaginal vault prolapse[21,120,121]. The treatment of rectocele, cystocele or vault prolapse on its own is not discussed here.

If a patient has gross genital and rectal prolapse, most authors recommend a combined simultaneous surgical treatment of both conditions. Zhioua *et al.*[120] reported combined surgery via an abdominal approach, fixing the uterus to the sacral promontory plus a rectopexy, with a 100 per cent success rate over a mean follow-up of 20 months. Bouret *et al.*[21], however, preferred a perineal approach. These authors performed perineal colporrhaphy plus a Delorme procedure with a success rate of 89–92 per cent. In general, most surgeons agree that surgery is the treatment of choice; the approach, however, usually depends on the preference and experience of the operator.

Recurrent rectal prolapse

Most surgical procedures described for rectal prolapse can achieve a satisfactory success rate and fairly low recurrence, with the exception of Thiersch anal encirclement. The true incidence of recurrence is, however, difficult to determine as there is an under-reporting by most authors. Also, the duration and method of follow-up are not stated in most series. It has been said that the longer the follow-up, the higher will be the incidence of recurrence of prolapse, which may occur up to 10 years after surgery. Mucosal prolapse, which occurs in 5–10 per cent of patients following surgery, is not generally considered a proper recurrence; it is easily treated by rubber band ligation or simple mucosal excision[96,122].

Surgeons who strongly advise perineal procedures for rectal prolapse claim that they are less major than abdominal procedures and have the advantage of repeatability. Thorne and Polglase[47] and Williams *et al.*[45] claim that a repeat perineal rectosigmoidoscopy for rectal prolapse can be performed easily, with low morbidity. Proponents of abdominal surgery for rectal prolapse, however, disagree. They claim that a repeat abdominal operation can also be performed and that abdominal procedures are less likely to create a recurrence to begin with.

Not all recurrent prolapses require surgery. A trial of conservative measures should first be advised, especially if the prolapse is small and asymptomatic. However, regardless of the nature of the surgery, there is a small group of patients who have undergone multiple operations for recurrent prolapses which have failed. There is also a group who remain severely symptomatic, for instance with continued incontinence, despite having a satisfactory correction of the anatomical rectal abnormality. These two groups of patients may benefit from the creation of a diverting colostomy, which is usually performed as a salvage procedure in less than 1 per cent of all patients with rectal prolapse[40].

Recent advances in management

The feasibility of laparoscopic surgery in the management of rectal prolapse has been demonstrated in several recent reports. In 1992 Berman[123] described a case of laparoscopic rectopexy in a 59-year-old woman using a newly designed sacral tacker, laparoscopic staplers and a Marlex mesh[124]. The laparoscopic sacral tacker was introduced transvaginally via a 12-mm trocar to fix the mesh into the sacral promontory. Laparoscopic hernia staplers were then used to fix the mesh to the side of the rectum. Munro *et al.*[125] recently described a case of laparoscopic rectopexy in a 74-year-old woman using a Marlex mesh and an Endopath Endoscopic stapler (J and J, Cincinnati, Ohio, USA). Senagore *et al.*[126] described six cases of laparoscopic anterior resection for the management of rectal prolapse. Although there were no postoperative deaths, there were two cases requiring open laparotomy. One patient had severe rectal scarring requiring conversion and the other had to be reoperated for severe trocar-site haemorrhage.

Other variations of laparoscopic techniques for the management of rectal prolapse have been described, all of which are similar to the conventional open approaches. These procedures involve fixation of the rectum to the presacral fascia with a foreign material (mesh) and/or various other resectional procedures[127–130]. The Cleveland Clinic Foundation has described the techniques of laparoscopic rectosacral fixation following rectal mobilization, a technique very similar to suture rectopexy in the conventional open setting[131]. This was performed in 13 consecutive patients with rectal prolapse without constipation. There was no evidence of recurrence of rectal prolapse at median follow-up of 12 months.

The use of laparoscopic techniques in the surgical treatment of rectal prolapse has been advocated as having several attractive features. Rectal prolapse is a benign condition and so causes no concern about resection margins. Furthermore, no resection may be needed in many instances. Mobilization of the rectum laparoscopically has been shown to be safe and feasible[123,125,126]. Although laparoscopic procedures for rectal prolapse are now possible, the complications associated with laparoscopic surgery need to be considered. Further investigations and prospective trials are needed to evaluate the safety and efficacy of this technique.

Conclusion

The surgical management of rectal prolapse has evolved from the historic Thiersch anal encirclement procedure to the present laparoscopic rectopexy. Selection of the most appropriate surgical operation continues to be problematic for surgeons. At this institution we prefer a laparoscopically-assisted resection rectopexy, especially in the young and fit patient with a significant history of constipation. A perineal procedure, such as Delorme or perineal rectosigmoidectomy, is usually reserved for the older, high-risk patient. One must remember that success in the management of rectal prolapse is not simply the correction of the physical and mechanical abnormality; functional aspects are also important. The ideal surgical technique should, therefore, be based not only on the elements of simplicity, recurrence and complications, but should also take into account the treatment or at least the alleviation of the functional disorder so commonly associated with rectal prolapse.

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Review

Colour flow duplex imaging of occlusive arterial disease of the lower limb

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Background The development of duplex ultrasonography and colour flow imaging has greatly extended the scope of non-invasive assessment of lower limb arterial disease. This review questions whether recent advances might allow colour duplex imaging to displace arteriography as the primary imaging modality for native vessel occlusive disease.

Methods A literature review was carried out based predominantly on a Medline database search of English language publications from 1985 to 1996.

Results Increasing evidence indicates that colour duplex ultrasonography can accurately image the lower limb native arterial tree, and that colour duplex imaging can replace diagnostic arteriography in a large proportion of patients.

Conclusion Arteriography should no longer be considered the gold standard of imaging of peripheral arterial occlusive disease. Future studies should concentrate on the efficacy of colour duplex sonography in guiding clinical decision making.

Recent technological advances in Doppler ultrasonography have raised the possibility that ultrasonography could displace arteriography as the primary imaging modality for the lower limb arterial tree. These advances have included the development of duplex sonography[1], which allows both accurate localization and quantification of occlusive disease, and of colour flow imaging[2], which by facilitating rapid assessment of blood flow along an arterial tree has greatly widened the scope of duplex scanning in clinical practice. This purpose of this article is to review the status of arteriography as the gold standard for imaging of lower limb occlusive arterial disease in the face of these advances. The limitations of arteriography are summarized, the use of duplex and colour flow to image occlusive disease is outlined, and the literature on colour flow duplex imaging of lower limb arterial disease is then reviewed. Finally, some future directions in the use of colour duplex in this area are anticipated. The review is based on an English language Medline literature search from January 1985 to September 1996 and excludes the use of ultrasonography for the investigation of aneurysmal disease and for graft surveillance.

Limitations of arteriography

Although arteriography is the traditional gold standard for peripheral arterial imaging, it has inherent limitations and a low, but significant, complication rate[3,4]. Perhaps its major drawback is that the information it provides is morphological, and so the haemodynamic impact of individual occlusive lesions can only be inferred. Moreover, arteriograms provide only a two-dimensional image of a three-dimensional disease, and the interpretation of arteriographic images is in part qualitative and subject to considerable interobserver variability[5]. Arteriograms may fail to show significant pathology altogether, most notoriously in the aortoiliac segment and at the origin of the profunda femoris artery, where disease is frequently eccentric. Although oblique views help in the assessment of the aortoiliac arteries, it has been shown that even if they are obtained, arteriography has an accuracy of only 70 per cent for the detection of significant stenoses when compared with intra-arterial pressure measurement (before and after papaverine)[6]; biplanar arteriography of the profunda femoris artery fails to identify up to 76 per cent of orifice stenoses compared with operative findings[6]. Notably, while the introduction of digital subtraction techniques has brought the advantages of relative speed and of a lower contrast load requirement, it does not improve image quality or definition when compared with conventional film-screen arteriography[7]. The clinical importance of these limitations of arteriography was highlighted by Sumner and Strandness[8] who reported that, when arteriography of the aortoiliac segment was used as the primary method of determining in which arterial segment surgery was to be performed, 30 per cent of limbs were not improved following aortofemoral bypass of a diseased aortoiliac segment, presumably because of overestimation of the haemodynamic significance of radiological disease.

In addition, the accuracy of distal lower limb imaging by arteriography is severely compromised by the presence of significant proximal disease because of underfilling of vessels, and may fail to demonstrate distal vessels suitable for reconstructive surgery in up to 70 per cent of patients with severe disease[9–11]. If diagnostic arteriography is used as the sole guide to the distal vasculature, amputation may be wrongly considered the only surgical option in a significant number of patients with critical limb ischaemia.

Egglin *et al.*[12] have recently audited the complication rate of peripheral arteriography in patients with claudication or limb-threatening ischaemia. The overall major complication rate was 2 per cent, a similar figure to that of earlier reports[3,4]. These complications compromised vascular injury (haematoma, false aneurysm,

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dissection and distal embolization), contrast reactions and contrast-induced renal failure, but excluded the less severe but relatively common complications of transient cardiovascular events (angina, vasovagal episodes) and postarteriographic pain in the distribution of the lateral cutaneous nerve of thigh. To these should be added the increased risk of wound and graft infection in a groin used for recent arteriographic access[13].

Arteriography as the gold standard

Arteriography is commonly held to be the diagnostic gold standard for imaging the lower limb arterial tree, and comparative studies of ultrasonography and arteriography have been based on this assumption[14–21]. This is unfortunate because it means that ultrasonography can at best, only be second best. Indeed, it could be argued that the status of arteriography as gold standard derives from its long established, tried and tested, place in clinical practice, rather than its inherent merits.

Colour flow imaging

While duplex imaging combines conventional B mode ultrasonography with pulsed Doppler ultrasonography to allow the selective gating of precise depths for quantitative Doppler frequency spectrum analysis within a vessel, colour Doppler imaging uses multiple gates to produce flow information from many depths simultaneously. This is then superimposed on the B mode image (*Fig. 1*). Unlike duplex ultrasonography, which produces the full spectrum of frequency shifts at any chosen gate, colour Doppler imaging assigns a single representative number (usually the mean Doppler frequency shift) to each site, which is then represented as different saturations of colours (red or blue depending on direction). Less saturation indicates regions with higher blood flow and deeper colours indicate slower flow; the absence of flow is coded as black[22]. The peak frequency shift, and therefore velocity, is not related directly to the mean frequency shift; moreover, colour displays of frequency shift are not corrected for the angle of insonation. Although this reduces its accuracy, colour Doppler imaging is primarily intended to provide qualitative information, and is best used as a guide to allow rapid identification of sites that warrant quantitative interrogation with pulsed Doppler ultrasonography. The use of colour flow imaging in this way increases the speed of duplex examination, and an aorta to popliteal examination of one limb can be performed in under 45 min using colour duplex scanning[17,21,23–25]. This represents a considerable improvement on black and white duplex technology, which can take up to 2 h[14,26]. Colour flow longitudinal imaging is also a useful guide to flow direction and enables accurate assessment of Doppler angles for velocity calculation while colour cross-sectional imaging is particularly helpful in reducing the number of errors due to slow flow[23].

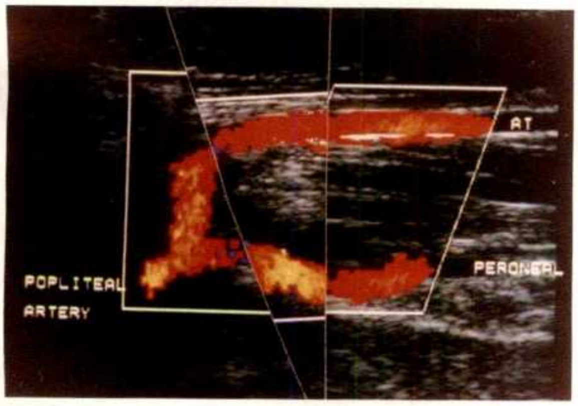

Fig. 1 Composite colour flow image showing blood flow in a popliteal artery on the left, and anterior tibial (AT) and peroneal arteries on the right. Velocity and direction of blood flow is represented as different saturations of colours; less saturation indicates higher blood flow and deeper colour indicates slower flow. The vessel lumen shows on B mode ultrasonography

It is noteworthy that while colour flow studies evaluating the lower limb arterial tree have been based to date on computation of mean Doppler frequency shift, alternative derivations of colour flow data have been introduced recently in order to overcome some of the image artefacts of colour Doppler scans. For instance, in the case of power Doppler ultrasonography, the colour map displays the integrated power of the Doppler signal instead of its mean Doppler frequency shift[27], and the hue and brightness of the colour is related to the number of blood cells producing the shift. Colour velocity imaging, on the other hand, is derived from a direct measurement of blood velocity[28]; clusters of blood cells with a recognizable 'signature' are tracked over micrometres, and the time and distance are measured directly to allow a velocity calculation. While these techniques may offer advantages over conventional colour Doppler scans, including less artefact, increased sensitivity and angle independence, their clinical superiority has yet to be demonstrated.

Ultrasonographic criteria used to identify significant arterial lesions in lower limb occlusive disease

Arterial occlusions are readily identified by an absence of flow both on colour and pulsed Doppler imaging. While colour flow imaging alone has been used to characterize stenotic lesions (*Fig. 2*)[29], it is non-quantitative and analysis of the Doppler velocity spectrum is more useful. At the site of a stenosis there is loss of the normal velocity waveform[30] (*Fig. 3*) with a reduction in the number of phases of flow, the absence of a peak systolic window and spectral broadening. However, the lack of specificity of these parameters makes them unreliable for use in localizing significant disease[26].

Peak systolic velocity

Most studies have used velocity data and, in particular, velocity ratios to grade stenoses, based on the principle that, since total flow at the site of a stenosis must be the same as the flow in the immediate prestenotic or poststenotic region, the relative change in velocity is directly related to the change in cross-sectional area of a vessel. In practice, the peak systolic velocity (PSV) is the variable most readily determined from the velocity spectrum (*Fig. 3*). The main advantage of the use of the PSV ratio is that it is a value which is independent of individual variations in blood pressure, vascular compliance and cardiac function[31]. Whenever possible, the velocity within a stenosis is compared with that just proximal to the

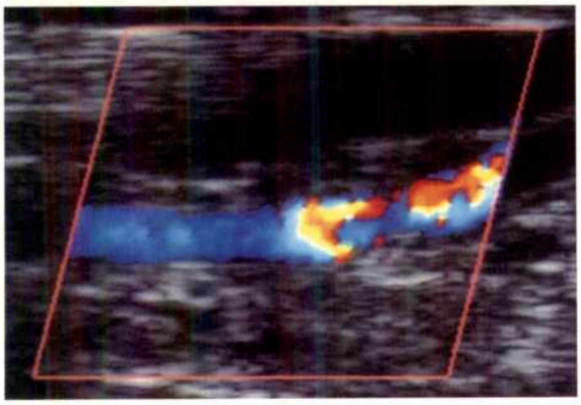

Fig. 2 Colour flow image showing a velocity increase indicative of a stenosis in a popliteal artery

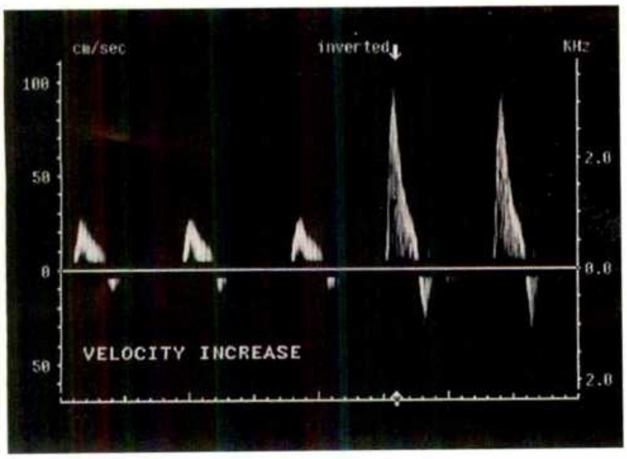

Fig. 3 Velocity waveform profile before and at the site of the popliteal stenosis shown on colour flow imaging in *Fig. 2*. Note that the velocity increase at the stenosis (arrow) is approximately 300 per cent indicating the stenosis to be significant

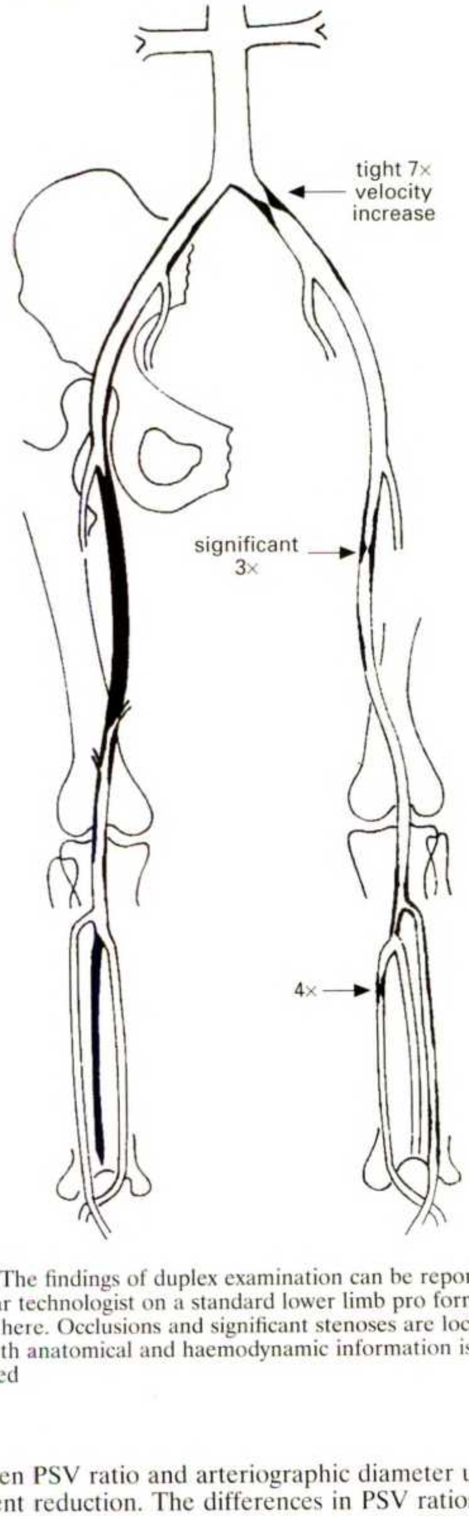

Fig. 4 The findings of duplex examination can be reported by the vascular technologist on a standard lower limb pro forma, as shown here. Occlusions and significant stenoses are localized, and both anatomical and haemodynamic information is therefore provided

stenosis, because the distal velocity waveform is distorted, particularly when stenoses are severe[31–33]. The grading of stenotic lesions using PSV ratios has been found to be reproducible both in experimental models of artery stenosis[33] and in patients with lower limb occlusive arterial disease[34].

Traditionally, a 50 per cent reduction or greater in arterial diameter (equivalent to a cross-sectional surface area reduction of 75 per cent) is considered to be associated with a significant fall in arterial blood flow and distal pressure[35–37], and a 50 per cent reduction in arterial diameter measured on arteriography has therefore been taken to denote a significant stenosis[17,18,26,38,39]. In practice, the PSV ratio that correlates with the presence of a 50 per cent lesion in the lower limb arterial tree has been considered by different investigators to be more than 1·4[24], 2·0[14,15,17,20,21,23,38,40], 2·4[31], 2·5[25,26,41], 2·8[42] or 3·0[34,43]. The optimum PSV ratio is derived from retrospective receiver operator characteristic (ROC) analysis. The sensitivity and specificity of a PSV ratio that predicts an arteriographic stenosis of 50 per cent is calculated for a range of possible ratios; the optimum PSV ratio is the one which gives the best combination[44]. Such a systematic analysis has been performed by only a proportion of these authors[21,24,26,31,34,38,42]; all showed a good correlation between PSV ratio and arteriographic diameter up to a 75 per cent reduction. The differences in PSV ratios selected by these authors presumably reflect differences in measurement techniques and in interpretation of arteriograms and ROC. In fact, the differences in sensitivity and specificity between a PSV ratio of 2·0 and 3·0 for predicting a 50 per cent stenosis are minor, and at a practical level are probably not important. In practice, the systematic use of PSV ratios to define significant stenoses and absence of flow on colour or pulsed Doppler scanning throughout the lower limb arterial tree allows the sonographer to produce both a haemodynamic and anatomical guide to disease (*Fig. 4*).

End diastolic velocity

The calculation of PSV ratios provides information which is directly related to changes in diameter at the site of a lesion and is essentially flow independent. Several investigators have evaluated the use of the absolute velocity, which is flow dependent and arguably a more haemodynamic variable[45]. The use of end diastolic velocity (EDV), in particular, has been promoted for the detection of arterial occlusive lesions[31,42,46–48], with the definition of absolute values of EDV which indicate a significant stenosis. However, the PSV ratio has been found to be a more sensitive and reliable index[26,49] of occlusive disease, presumably because of the effect of wide individual variations in blood pressure, vascular compliance and cardiac function.

Flow-related spectral analysis

To obtain more information about the haemodynamic impact of an occlusive lesion, attempts have been made to use the Doppler velocity spectrum to derive flow data[47,50]. This requires assumptions to be made about the conditions of flow within a diseased blood vessel which simplify the complex interactions of variables such as viscous energy, flow pulsatility, vascular geometry and vessel compliance. Although meaningful flow data have been collected in experimental models[51,52], determination of flow or pressure changes from the frequency spectrum has had limited success in clinical practice[16,47,53].

Duplex imaging of native vessel occlusive disease

Most studies have compared duplex assessment of the lower limb with conventional arteriography, accepting arteriography as the gold standard, and have used PSV ratios to characterize stenoses (*Table 1*). A meta-analysis of such studies has concluded that duplex scanning could replace diagnostic arteriography in a substantial number of patients[54].

Iliac segment

Although the depth and angles at which iliac vessels run make this segment difficult to insonate, in experienced hands sonography is none the less technically successful in over 90 per cent of cases[15,17,26,43,47,49,55]. The problems caused by the presence of overlying gas-filled loops of bowel may be reduced by fasting patients before examination, or by the use of bowel preparation agents[56]. Numerous studies have found that there is good correlation between duplex ultrasonography and arteriography in this segment (*Table 1*), pooled estimates of sensitivity and specificity for detection of a stenosis of more than 50 per cent by duplex sonography are 80 and 95 per cent respectively, and for the detection of occlusions 94 and 99 per cent respectively[54]. Compared with intra-arterial pressure measurements, however, duplex scanning, like arteriography, appears to miss up to 25 per cent of stenoses (*Table 1*), neither modality consistently outperforming the other[45]. Whether this represents a true limitation of duplex technology or rather an overestimation of disease by pressure measurements is uncertain and again raises the issue of the gold standard. The use of duplex ultrasonography to estimate pressure gradients across aortoiliac lesions has met with limited success[47] and the use of flow related indices, such as the change in absolute PSV and EDV during hyperaemic states, may be of more value and merits further investigation[47,57].

Although analysis of femoral artery waveforms to predict the presence of aortoiliac disease has its limitations[32,58–60], there remains an interest in its use for the rapid assessment of aortoiliac segments[61–63]. While subjective assessment of the femoral artery waveform, and specifically of the presence of reversed diastolic flow, has been found in some studies to have a sensitivity of 87–96 per cent for significant iliac lesions[64,65], it has also been shown that waveforms may normalize a short distance downstream from significant stenoses, and are affected by distal disease[58]. Recently, Currie *et al.*[48] have demonstrated that the sensitivity of femoral waveform analysis is increased by postocclusive hyperaemia and have characterized a postocclusive duplex test for rapid outpatient screening of iliac segments.

Femoropopliteal segment

This segment is more superficial and so presents fewer technical problems than the aortoiliac segment. It can be scanned at a higher Doppler signal frequency (5 MHz)

Table 1 Sensitivity and specificity of aortoiliac and femoropopliteal duplex scanning compared with arteriography or intra-arterial pressure measurement

				Iliac segment		Femoropopliteal segment	
Reference	Year	No. of limbs	Gold standard	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Jager *et al.*[14]	1985	54	Arteriography	81	100	64	84
Kohler *et al*[15]	1987	55	Arteriography	89	90	84*	93*
Langsfeld *et al.*[16]	1988	46	Arteriography	82	93	–	–
Legemate *et al.*[49]	1989	80	IAPM	73 (71)	97 (94)	88	98
de Smet and Kitslaar[43]	1990	90	IAPM	77	88	–	–
Legemate *et al*[26]	1991	108	IAPM	75 (75)	89 (89)	–	–
Moneta *et al.*[17]	1992	286	Arteriography	89	99	83	98
Moneta *et al.*[18]	1993	151	Arteriography	88	97	93	100
Whelan *et al.*[19]	1992	100	Arteriography	81	100	97	98
Karacagil *et al.*[20]	1994	68	Arteriography	83	96	96	90
Sensier *et al*[21]	1996	148	Arteriography	65	96	86	97

Values in parentheses represent equivalent comparison between arteriography and intra-arterial pressure measurement (IAPM). *Applies to superficial femoral artery only which enhances the signal quality that is obtained. Overall, the technical success rate for this segment has been reported to approach 100 per cent[24,26,29], inclusive of the profunda femoris artery, which can be reliably assessed both in the presence or absence of superficial femoral artery occlusion[17,49,66]. Again, good correlation has been reported between duplex scanning and arteriography (*Table 1*). Pooled estimates of the sensitivity and specificity of duplex evaluation for detection of a stenosis of more than 50 per cent for this segment are 82 and 96 per cent respectively, and for the detection of occlusions 90 and 97 per cent respectively[54] As in the aortoiliac segment, duplex scanning has a high negative predictive value so that significant lesions can be reliably excluded.

For superficial femoral artery occlusions there is good overall agreement between duplex assessment and arteriography with respect to occlusion length[67–69]. There is, however, a tendency for the former to measure slightly shorter occlusion lengths than arteriography[38,68,69]. This probably reflects overestimation of occlusion length by arteriography due to underfilling above and below occlusions[38].

Duplex scanning has also been advocated as a useful diagnostic investigation for patients in whom popliteal entrapment syndrome is suspected, using active plantar flexion as a provocation manoeuvre[70,71]. However, the finding that such a provocation may result in symptom-free compression of the popliteal artery in healthy volunteers[72] has cast doubt on the reliability of this test and suggests that the diagnosis should not be made on the basis of duplex scanning alone.

Infrapopliteal arteries

There have been relatively few studies that have investigated the efficacy of duplex ultrasonography at imaging infrapopliteal disease[20,73], although the intrapopliteal arteries have been shown to be accessible for assessment in healthy volunteers[30]. Current evidence suggests that infrapopliteal scanning may be a useful way of identifying both occlusions[17] and stenoses[29]. Technical success rates of 91–100 per cent for visualizing the anterior and posterior tibial arteries and 83–90 per cent for the peroneal artery have been reported[17,29]; none the less calcification of vessels, particularly in diabetics, may cause particular problems at this level[69].

Effect of multilevel disease on accuracy of duplex mapping

Attention has been drawn to a possible effect of multilevel disease on the sensitivity of duplex scanning[39,74]. Since the use of peak velocity ratios corrects for segment to segment variation in velocity, the presence of upstream disease should not affect the sensitivity of the flow-dependent PSV ratio. Indeed, in studies that have used PSV ratios to classify disease, adjacent disease has not been found to have a detrimental effect[14,15,17,26,31,75,76]. The reported reduced sensitivity of duplex scanning for defining multilevel disease[39,74] may reflect a diagnostic emphasis on the visual interpretation of the Doppler spectrum or on absolute PSV, both of which are influenced by neighbouring disease[26].

Colour duplex scan-guided intervention

Duplex imaging is of particular value in selecting patients for percutaneous transluminal angioplasty (PTA); its use markedly reduces the requirement for diagnostic arteriography in selected patients, particularly those with superficial femoral artery lesions[38,67,68,77–79]. It has the further advantage of providing information that may assist in determination of the arterial puncture site and route of access for PTA In cases of superficial artery occlusion, two factors that may influence selection for PTA are the length of the occlusion and the presence of a patent superficial femoral artery stump. While occlusion lengths measured by duplex scan tend to be shorter than those measured by arteriography, the important practical point is that the former will not exclude patients from consideration for PTA[38]. Colour duplex scanning appears to be reliable at discriminating the presence or absence of a stump, even in the presence of proximal occlusions of this segment[69,80]. The use of duplex sonography to evaluate the haemodynamic effect of PTA has been examined[81–83]; two of these studies indicated that a residual PSV gradient of more than 2 in the first week after PTA was predictive of a poor outcome, even if on arteriography PTA was considered successful[82,83]. The feasibility of performing PTA guided by colour duplex imaging alone has been demonstrated[84,85]. This allows the immediate outcome of angioplasty to be judged by haemodynamic rather than purely morphological improvement. Whether this approach may lead to better results than arteriographically-directed PTA remains to be determined.

The value of surveillance of stenotic lesions in patients whose symptoms do not warrant PTA is hard to determine in an area lacking in controlled studies[86], but it has been observed that a PSV ratio of greater than 3·0 portends occlusion which may not be amenable to treatment by PTA[87]. There is, however, no evidence that PTA of such lesions is beneficial and so surveillance, as well as treatment, of subclinical stenoses cannot currently be justified.

The use of duplex scanning as the primary imaging modality in patients with occlusive disease was examined prospectively in 112 consecutive symptomatic patients by Elsman *et al.*[25]. Although arteriography was performed in a relatively large number of these patients (39 per cent), it gave additional information in only 41 per cent of cases. The authors concluded that the integrated use of duplex scanning in the assessment of occlusive disease would allow a substantial proportion of patients to avoid arteriography. Indeed eight of 32 patients were referred for surgery on the basis of colour duplex scanning alone. A recent study of the results of adopting colour duplex assessment as the primary imaging modality in a consecutive series of 329 symptomatic patients showed that management decisions were based on colour duplex information alone in 98 per cent of cases[69]. Moreover, the safety of performing lower limb surgery using colour duplex scanning as the sole imaging modality has also been confirmed in a consecutive series of 75 patients undergoing a wide range of arterial reconstruction[88].

Colour duplex imaging *versus* magnetic resonance angiography

Although several investigators have reported on the use of magnetic resonance angiography (MRA) to assess the lower limb arterial tree, the comparative standard of MRA has been conventional contrast angiography[89–92] and detailed comparisons between duplex scanning and MRA are lacking. Like ultrasonography, MRA has the potential to provide both haemodynamic and morphological information[93,94], although to date only anatomical images that are akin to contrast arteriography have been used widely. There have been favourable reports of its ability to define both proximal[91] and distal disease[89] in low flow states[91], although in the only study that has included duplex examination, the latter modality proved to be the more sensitive at defining aortoiliac disease[63]. Although MRA can accurately image the lower limb arterial tree it seems unlikely that it will pose a serious challenge to duplex technology because the latter modality is considerably cheaper; it can also be transported easily to the bedside or to the outpatient department[69].

Future developments

While the use of duplex and colour flow imaging to image disease at the femoropopliteal level has been widely accepted, there remain reservations about its efficacy at the aortoiliac and intrapopliteal levels. Future technological advances are likely to lead to further improvement in resolution of colour duplex images which should itself enhance the accuracy of quantitative measurement from the Doppler spectrum, and so improve the results of colour duplex arterial assessment generally. This may apply particularly to the aortoiliac segment where the depth and direction of the vessels to be investigated is challenging. While the evidence suggests that results of colour duplex assessment of the aortoiliac segment can match those of arteriography[54], there is little doubt that a high technical success rate can be achieved only by an experienced vascular technologist.

At the infrapopliteal level, further work is required to evaluate the efficacy of colour duplex scanning in the assessment of occlusive disease. It has already been demonstrated that the assessment of crural vessels and their continuity with the pedal arch by continuous Doppler ultrasonography, using the techniques of either pulse-generated run-off[95] or dependent Doppler insonation[96], yields up to 25 per cent more recognition of patent calf vessels than both conventional arteriography and intra-arterial digital subtraction angiography[97–100]. It is likely that, while the most suitable distal vessel to receive a graft may be selected by one of these methods, the level for insertion of a graft may best be selected by colour duplex scanning.

There is now enough evidence to suggest that arteriography should no longer be considered the gold standard; future studies of colour duplex assessment should examine its ability safely and accurately to guide therapeutic vascular interventions rather than compare it with arteriography[25,69]. However, lower limb duplex ultrasonography requires highly skilled and dedicated technologists, and it should be emphasized that if this modality is to replace diagnostic arteriography successfully, the provision of adequate training is of the utmost importance.

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Review

Systemic inflammatory response syndrome

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Background Localized inflammation is a physiological protective response which is generally tightly controlled by the body at the site of injury. Loss of this local control or an overly activated response results in an exaggerated systemic response which is clinically identified as systemic inflammatory response syndrome (SIRS). Compensatory mechanisms are initiated in concert with SIRS and outcome (resolution, multiple organ dysfunction syndrome or death) is dependent on the balance of SIRS and such compensatory mechanisms. No directed therapies have been successful to date in influencing outcome.

Method This review examines the current spectrum and pathophysiology of SIRS.

Results and conclusion Further clinical and basic scientific research is required to develop the global picture of SIRS, its associated family of syndromes and their natural histories.

One of the most frequent and serious problems confronting clinicians is the management of infection and the systemic responses that it induces. From 100 000 to 300 000 patients develop bacteraemia annually in the USA[1] and shock is a complication of sepsis in almost 50 per cent of these patients, with a mortality rate of 40–60 per cent. The clinical features associated with sepsis were noted by Hippocrates in 400 BC when he remarked that 'in acute diseases, coldness of the extremities is a very bad sign'. Sepsis remains a clinical challenge for the surgeon in and out of the critical care unit. The incidence of sepsis has been increasing for the past 60 years and is the most common cause of death in critical care units in the USA and Europe. Although remarkable progress has been made in defining the pathophysiology of this disease, the terminology associated with research in the field has been confusing. In an attempt to stratify the spectrum of sepsis, a consensus conference of the Society of Critical Care Medicine and the American College of Chest Physicians was held in August 1991 to produce a series of universal definitions for the systemic inflammatory response syndrome (SIRS), sepsis and other clinical conditions related to sepsis[2] (*Fig. 1*). SIRS was developed to imply a clinical response arising from a non-specific insult and includes two or more defined variables (*Table 1*). Sepsis is defined as SIRS with a documented infection. The sequela of SIRS/sepsis is multiple organ dysfunction syndrome (MODS) which can be defined as failure to maintain homeostasis without intervention (*Figs 2* and *3*). Primary MODS is a direct result of a well defined insult, while secondary MODS develops not in direct response to the insult but as a consequence of a host response. MODS is recognized as a sequel of SIRS. While nearly all patients with sepsis develop dysfunction of one organ system, multiple organ dysfunction occurs in about 30 per cent of patients with sepsis. Similarly, MODS can be identified in over 30 per cent of patients with trauma, 24 per cent of those with acute pancreatitis and nearly 40 per cent of patients with burns.

There is a continuum from the development of SIRS to the onset of sepsis and progression to septic shock and multiple organ dysfunction. In a prospective survey of admissions to a tertiary care facility in the USA, 68 per cent of patients met the criteria for SIRS[3]. Of these, 26 per cent developed sepsis, 18 per cent developed severe sepsis and 4 per cent developed septic shock within 28 days. The interval between the identification of SIRS and the development of sepsis was inversely correlated with the number of SIRS criteria initially identified (two, three or four). Mortality rates in that study were 7, 16, 20 and 46 per cent respectively for SIRS, sepsis, severe sepsis and septic shock. Similar trends have been identified in the Italian SEPSIS study[4]. It is important to note that identification of SIRS alone in a patient in the intensive care unit has a poor specificity for predicting the development of sepsis and septic shock[5]. However, there is an increasing incidence of organ system failure as

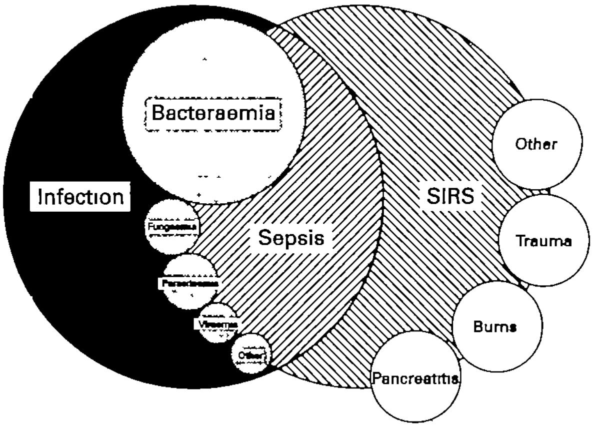

Fig. 1 The inter-relationship between sepsis, systemic inflammatory response syndrome (SIRS) and infection. Note that bacteraemia may or may not denote sepsis. ▨, Blood-borne infection. (Reproduced from reference 2 with permission from the Society of Critical Care and Williams and Wilkins, Baltimore, Maryland, USA)

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patients progress from SIRS to septic shock[3]. Another study has shown that the use of SIRS criteria in patients with trauma to predict the onset of MODS or infection is not reliable[6].

Physiology of inflammation

The innate ability of the body to defend itself is based on three elements: external barriers against invasion and tissue injury, non-specific systems against foreign pathogens and debris, and antigen-specific responses to foreign pathogens[7]. Inflammation is the body's initial non-specific response to tissue injury produced by mechanical, chemical or microbial stimuli. Inflammation is a rapid highly amplified controlled humoral and cellular response: the complement, kinin, coagulation and fibrinolytic cascades are triggered in tandem with the activation of phagocytes and endothelial cells[8]. This local response may

Table 1 Criteria for systemic inflammatory response syndrome, sepsis and multiple organ dysfunction syndrome

SIRS	Systemic inflammatory response is a characteristic clinical response manifested by two or more of the following: Temperature above 38°C or below 36°C (rectal) Heart rate above 90 beats per min Respiratory rate above 20 breaths per min or Pa_{CO_2} less than 4·3 kPa WBC count above 12 000 cells per mm^3, below 4000 cells per mm^3 or 10 per cent immature (bands) forms
Sepsis	SIRS with documented infection
Severe sepsis	SIRS with documented infection and haemodynamic compromise
MODS	A state of physiological derangement in which organ function is not capable of maintaining homeostasis

SIRS, systemic inflammatory response syndrome; Pa_{CO_2}, arterial partial pressure of carbon dioxide; WBC, white blood cell; MODS, multiple organ dysfunction syndrome. (Reproduced from reference 2 with permission from the Society of Critical Care and Williams and Wilkins, Baltimore, Maryland, USA.)

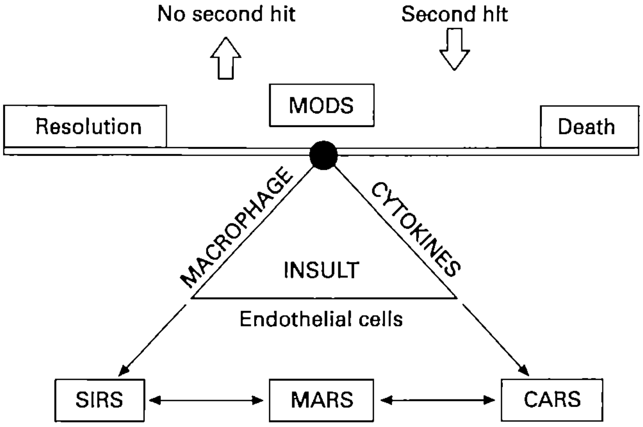

Fig. 2 The pendulum and spectrum of systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS) and mixed antagonist response syndrome (MARS). Tissue insult/injury triggers a triad of systems encompassing the macrophage cytokines and endothelial cells. This results in SIRS/CARS/MARS which results in end-organ dysfunction. This can progress to multiple organ dysfunction syndrome (MODS) particularly when aggravated by a second hit (another tissue insult/injury), or can move towards resolution particularly when second hits are avoided

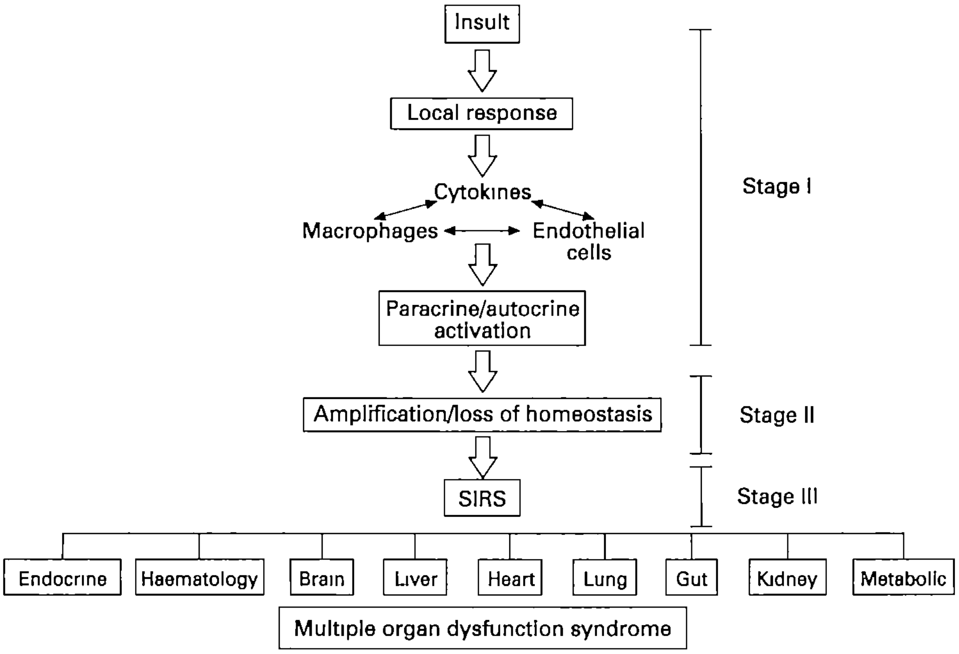

Fig. 3 Development of systemic inflammatory response syndrome (SIRS). Stage I: in response to an insult, the local environment produces cytokines which are primarily intended to evoke an inflammatory response, promote wound repair and recruit the cells of the reticuloendothelial system. In stage II, small quantities of cytokines are released into the circulation to enhance the local response. Macrophages and platelets are recruited and growth factor production is stimulated. The acute-phase response is tightly controlled by a simultaneous decrease in proinflammatory mediators and release of endogenous antagonists. This continues until the wound is healed, the infection has resolved and homeostasis is restored. Occasionally homeostasis is not re-established and stage III (SIRS) develops. The sequela of SIRS/sepsis is multiple organ dysfunction syndrome

be considered benign as long as the inflammatory process is regulated appropriately to keep cells and mediators sequestered. There are four major events in the inflammatory process: vasodilatation, increased microvascular permeability, cellular activation/adhesion and coagulation. Vasodilatation and increased microvascular permeability at the site of injury increase locally available oxygen and nutrients, and produce heat, swelling and tissue oedema. The local haemodynamic changes give rise to the four classical symptoms associated with local inflammation: rubor (erythema), tumor (oedema), calor (heat) and dolor (pain). The normal physiological response to stress and injury results in a series of cardiovascular changes (increases in heart rate, contractility and cardiac output) and neuroendocrine changes (increased release of catecholamines, cortisol, antidiuretic hormone, growth hormone, glucagon and insulin). There is an increased fluid requirement due to 'third spacing'. The major metabolic change that occurs in response to inflammation is an initial increase in oxygen consumption. The arteriovenous difference in oxygen content will remain normal provided oxygen delivery is maintained; however, anaerobic metabolism will ensue if the body fails to meet the oxygen deficit[9–11]. Concurrent with the increased metabolic responses, there is a fall in systemic vascular resistance. Unless a second insult occurs, the peak effect of these local and systemic physiological changes occurs within 3–5 days after the initial stimulus and abates by 7–10 days. Clinically, a progressive decrease in 'third space' fluid requirement, and a downward trend in pulse and temperature followed by spontaneous diuresis, herald an uncomplicated and improving clinical course.

Cytokines are the physiological messengers of the inflammatory response and the principal molecules involved are tumour necrosis factor (TNF) α, interleukins (IL-1 and IL-6), interferons and colony stimulating factors (CSFs). Polymorphonucleocytes (PMNs), monocytes/macrophages and endothelial cells are the cellular effectors of the inflammatory response. Leucocyte activation leads to increased leucocyte aggregation and tissue infiltration within the microcirculation where these leucocytes (PMNs and macrophages) undergo a respiratory burst, and increase their oxygen consumption and production of cytokines and other inflammatory mediators[12]. Endothelial cells exposed to this milieu of humoral and leucocyte-derived factors also become activated, and commence the expression of several adhesion molecules and receptors on their surface along with the synthesis and secretion of additional cytokines and secondary inflammatory mediators, including prostaglandins, leukotrienes, thromboxanes, platelet activating factor (PAF), oxygen free radicals, nitric oxide and proteases (cathepsin, elastase). Many of these secondary inflammatory mediators are also produced by leucocytes. The presence of activated endothelial cells and the enhanced cytokine milieu results in activation of the coagulation cascades which leads to local thrombosis minimizing blood loss and the walling off of injured tissues, thus attempting physiologically to isolate the inflamed areas.

Pathophysiology of systemic inflammatory response syndrome

Osler said 'patients die not of their disease, they die of the physiological abnormalities of their disease'. Localized inflammation is a physiological protective response which is generally tightly controlled by the body at the site of injury. Loss of this local control or an overly activated response results in an exaggerated systemic response which is clinically identified as SIRS. SIRS may be initiated by infection (viruses, bacteria, protozoa and fungi) or by non-infectious causes such as trauma, autoimmune reactions, cirrhosis and pancreatitis (*Fig. 1*). In a recent article, Bone[13] proposed that there were three stages in the development of SIRS (*Fig. 3*). In Stage I, in response to an insult, the local environment produces cytokines which are primarily intended to evoke an inflammatory response, promote wound repair and recruit the cells of the reticuloendothelial system. In Stage II small quantities of cytokines are released into the circulation to enhance the local response. Macrophages and platelets are recruited and growth factor production is stimulated. An acute-phase response is initiated and is tightly controlled by a simultaneous decrease in proinflammatory mediators and release of endogenous antagonists. These mediators keep the initial inflammation response in check both by downregulating cytokine production and by counteracting the effects of cytokines already released. This continues until the wound is healed, the infection resolved and homeostasis is restored. Occasionally homeostasis is not re-established and Stage III (SIRS) develops (*Fig. 3*). With the failure of homeostasis, a massive systemic reaction begins. The predominant effects of cytokines become destructive rather than protective. The flood of inflammatory mediators triggers numerous humoral cascades and results in sustained activation of the reticular endothelial system with loss of microcirculatory integrity and insults to various distant end organs (*Figs 3* and *4*).

Although flow and permeability changes at the local area increase nutrient delivery, uncontrolled systemic vasodilatation produces a sustained decrease in systemic vascular resistance and hypotension, while increased systemic vascular permeability results in significant extravascular third spacing. Coupled to these events there is depression of myocardial contractility which may be due to the effect of paracrine nitric oxide production and coronary non-occlusive microvascular damage and myocyte injury[14]. These phenomena make it difficult to volume resuscitate a hypotensive patient adequately. In combination, the loss of peripheral vascular tone and the loss of volume into extravascular spaces negate the normal homeostatic response necessary to maintain oxygen delivery and correct the abnormal arteriovenous difference in oxygen content[10,15]. The inability physiologically to correct these adverse responses results in end-organ hypoperfusion, oedema, initiation of anaerobic metabolism and end-organ dysfunction.

Early in the SIRS process, large numbers of leucocytes become adherent to the activated endothelial cells of the vessel wall and can interrupt the microcirculatory flow[16]. Leucocyte adherence is partially related to an increase in the number of adhesion molecules present on the endothelial cells. TNF-α, IL-1 and many other inflammatory mediators trigger endothelial cells to express new or increased numbers of adhesion molecules. In addition to the mechanical interruption of microcirculatory flow, activated leucocytes can damage adjacent endothelial cells and the surrounding extravascular tissue. TNF-α and IL-1 are considered primary proinflammatory mediators and induce a range of secondary proinflammatory mediators called chemokines.

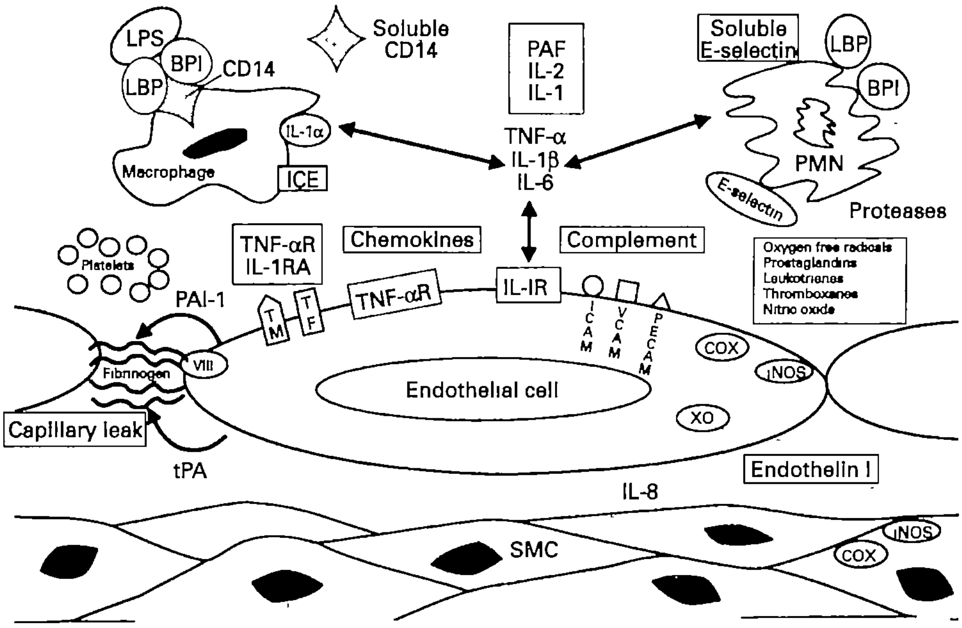

Fig. 4 The cellular biology of systemic inflammatory response syndrome. Lipopolysaccharide (LPS) can interact with lipopolysaccharide binding protein (LBP) and bactericidal/permeability increasing protein (BPI). LBP in turn interacts with the LPS receptor CD14 inducing cytokine expression. Tissue insult/injury triggers a triad of effector systems: macrophages, cytokines and endothelial cells. The principal cytokines are tumour necrosis factor (TNF) α, interleukin (IL) 1 and IL-6. Polymorphonucleocytes (PMNs), macrophages and endothelial cells are the cellular effectors of the inflammatory response. Endothelial cells exposed to this milieu of humoral and leucocyte-derived factors also become 'activated' and commence the expression of several adhesion molecules and receptors on their surface and the synthesis/secretion of additional cytokines and secondary inflammatory mediators. ICE, interleukin converting enzyme; TNF-αR, TNF-α receptor; IL-1R, IL-1 receptor; IL-1RA, IL-1 receptor antagonist; PAF, platelet activating factor; TM, thrombomodulin; TF, tissue factor; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule 1; PECAM, platelet–endothelial cell adhesion molecule; COX, cyclooxygenase; XO, xanthine oxidase; iNOS, inducible nitric oxide synthase; SMC, smooth muscle cell

Two major groups of chemokines have been categorized, the CXC subfamily which is chemotactic for neutrophils, and the CC subfamily which is chemotactic for monocytes[17].

Activated endothelial cells express multiple factors (e.g. tissue factor, platelet–endothelial cell adhesion molecule, thromboxane (TX) A_2) which convert their local environment from a neutral coagulant environment to a procoagulant one. In addition, TNF-α triggers the coagulation cascades by activation of the extrinsic pathway[18]. Endotoxin triggers both the coagulation and fibrinolysis cascades[19]. Factor XII has a central role in the pathogenesis of septic shock activated by the peptidoglycan residues and technoic acid from the cell wall of Gram-positive organisms as efficiently as by lipopolysaccharide (LPS) and lipid A from Gram-negative organisms[20]. Factor XIIa triggers both the intrinsic coagulation pathway through activation of Factor XI, and induces both endothelial cells and macrophages to produce tissue factor, which in turn activates the extrinsic coagulation pathway. Antibodies to tissue factor prevent LPS-induced disseminated intravascular coagulation in rabbits[21]. Endotoxaemia causes an increase in the levels of tissue plasminogen activator (tPA) in plasma which is rapidly counterbalanced by the release of plasminogen activator inhibitor (PAI) 1[22]. In sepsis, plasma levels of protein C and antithrombin III decrease and there are increased plasma levels of PAI-1. Plasma thrombomodulin, which is derived from degradation of endothelial cell membrane thrombomodulin, is also increased in SIRS[23]. The multiple actions of thrombin and the failure of natural inhibitory mechanisms, such as antithrombin III, protein S, protein C and plasma fibrinolysis inhibitors, also contribute to this process[24]. This procoagulant environment coupled to endothelial cell injury predisposes to the development of excessive microthrombi, further obstructing local blood flow and exacerbating end-organ dysfunction.

These potentially destructive systemic and regional responses in SIRS (increased peripheral vasodilatation, excessive microvascular permeability, accelerated microvascular clotting, leucocyte/endothelial cell activation) contribute to the development of profound pathophysiological changes in the various organs, and are considered the major aetiological factors in the development of septic shock, disseminated intravascular coagulation[25], adult respiratory distress syndrome (ARDS) and other end-organ dysfunction leading to MODS. Linked to these end-organ failures are the metabolic and nutritional effects of an activated cytokine milieu which produces fever, hypermetabolism, anorexia, protein catabolism, cachexia, and altered fat, glucose and trace mineral metabolism[26]. These processes are accelerated if a second insult such as shock, infection or ischaemia follows the initial injury.

Mediators of systemic inflammatory response syndrome

The mediator response in SIRS may be divided into four phases based on the cytokine/cellular response: induction, triggering of cytokine synthesis, evolution of cytokine cascade and elaboration of secondary mediators with ensuing cellular injury. Of the multitude of mediators operating in SIRS/sepsis, the three most influential appear to be TNF-α, IL-1 and IL-6. Raised serum levels of TNF-α and IL-6 are seen in subjects challenged with endotoxin and in patients with sepsis[27,28]. Whereas absolute levels of TNF-α and IL-6 are crudely predictive of death from septic shock, persistence of TNF-α and IL-6 in serum is highly predictive of the development of MODS and death[29,30]. The deleterious host response to infection has been dissected extensively with regard to Gram-negative bacterial sepsis and endotoxaemia leading to cytokine release. Specific attention has been directed toward TNF-α, IL-1 and IL-6 because their release has been most closely associated with morbidity and death[28]. IL-6 also appears to be associated with the host septic response, probably being released in response to secretion of either TNF-α, IL-1 or both cytokines. Abrogation of IL-6 using IL-6 antibodies has been associated with improved survival in animal models of Gram-negative bacterial sepsis or in models in which TNF-α is infused. Infusion of IL-6 itself does not have any effect. Similarly, although direct injection of IL-8 does not produce adverse effects, raised levels of this cytokine have been demonstrated following a challenge of either Gram-negative bacteria or endotoxin in experimental models, but a great deal of information suggests that this cytokine acts to potentiate the effects of other mediators.

The events following endotoxin exposure provide a good model on which to discuss the four phases of SIRS. Endotoxin, shed from the bacteria as they multiply or die, is one of the most powerful triggers of SIRS by stimulating phagocytic cells, particularly macrophages, to synthesize TNF-α and IL-1, to activate the complement/coagulation cascades and to induce endothelial cell activation. Cytokines are not stored and their synthesis requires gene transcription or translation of messenger RNA (mRNA). In the baboon, after exposure to endotoxin, serum levels of TNF-α peak at 1·5 h, IL-1β at 3 h and interferon (IFN) γ at 6 h[31]. In humans, infusions of either endotoxin, TNF-α or IL-1 cause myalgia, chills, headache, nausea and tachycardia following which cardiac output increases and systemic vascular resistance falls[32]. These symptoms begin 90–120 min after endotoxin exposure, concurrent with the time TNF-α levels rise. In contrast, these symptoms occur almost immediately after TNF-α infusion. Although some investigators have identified the presence of raised IL-1 levels after endotoxin exposure, this is not a consistent finding. Similarly, increased IFN-γ concentrations have not been demonstrated after an infusion of endotoxin in humans. These studies have been extended to profile the role of cytokines in patients who develop sepsis. Raised levels of TNF-α, IL-1, IL-6, IL-8 and IFN-γ have been reported to occur in groups of patients with sepsis, but the pattern of cytokine abnormalities in each individual may not be similar to that which would be expected based on data obtained from numerous animal studies[28]. Furthermore, the correlation of raised specific cytokines with death has not been demonstrated uniformly. In addition to the circulating levels of cytokines there are increased serum concentrations of cytokine antagonists (soluble TNF-α receptor and IL-1 receptor antagonist) and antiendotoxin core antibodies in patients with SIRS; these antagonists were present at concentrations 30–100 000-fold greater than their respective cytokines[33]. There are increased complement levels in sepsis, and these have been associated with fatal outcome in both Gram-positive and Gram-negative septic shock[34–36]. Survivors of SIRS/sepsis show improvement over the first 72 h in high molecular weight kininogen concentrations and higher than normal Factor V values compared with non-survivors. Persistently low serial Factor XII, high molecular weight kininogen and Factor V are associated with a poor prognosis[37]. Enhanced levels of C-reactive protein are seen in SIRS/sepsis and a decrease in C-reactive protein level precedes clinical resolution of the condition[38].

Endotoxin

The Gram-negative bacterial wall consists of inner and outer membranes, the latter of which contains many proteins as well as LPS. LPS consists of three regions: the O antigen polysaccharide, the core and the lipid A regions. The lipid A region is considered to be responsible for the majority of the toxicity. LPS can interact with mammalian cell membranes by several different types of receptor, including CD11/18, CD14, the acetyl-low density lipoprotein scavenger receptor, other less well defined membrane proteins and by non-specific cell membrane lipid interactions. There is a family of serum proteins which possesses LPS binding sites, of which lipopolysaccharide binding protein (LBP) and bactericidal/permeability increasing protein (BPI) are the most researched[39,40]. Interaction of LPS with CD14 receptors requires the LPS first to bind to LBP[41]. CD14 response to LPS–LBP complex is enhanced compared with that to LPS alone. The enhancing effect of LBP provides an early warning mechanism for the presence of low concentrations of endotoxin. Blockade of CD14 offers an additional therapeutic option in controlling the cytokine response[42]. BPI binds to LPS and prevents macrophage activation, and is protective in rodent models of lethal endotoxaemia[41]. A soluble CD14 receptor has been identified and probably participates in all phases of SIRS with its ability to induce LPS sensitivity in cells normally insensitive to LPS (e.g. smooth muscle cells)[43].

Tumour necrosis factor α

Various cells of the reticular endothelial cell system, such as monocytes, pulmonary macrophages, hepatic Kupffer cells and peritoneal macrophages produce TNF-α[44]. The expression of TNF-α is tightly controlled both at transcriptional and translational levels. The half-life of circulating TNF-α is short, 14–18 min, and it is degraded in several organs including the liver, skin, gastrointestinal tract and kidney. Specific receptors for TNF-α are found on a wide variety of cells and a maximal biological response is elicited by occupancy of as few as 5 per cent of these receptors[45,46]. The systemic and tissue-specific cellular mechanisms of TNF-α are dependent on its direct effects as well as the release of other soluble mediators from host cells. It elicits the release of neutrophils from the bone marrow and initiates neutrophil margination by inducing expression of adhesion molecules, promoting their transendothelial passage and activation (degranulation, production of superoxides and release of lysozymes). TNF-α promotes differentiation of monocytes and macrophages, and induces the activation of macrophages. It stimulates the synthesis of acute-phase proteins and activates the common pathway of the coagulation and complement systems. TNF-α produces a dose-dependent increase in endothelial procoagulant activity and may inhibit thrombomodulin expression at the endothelial cell surface. It induces IL-1 release from endothelial cells and macrophages, while IL-1 subsequently stimulates the biosynthesis of other cytokines. The presence of IL-1 and other cytokines appears to enhance the sensitivity of tissues to the effects of TNF-α[47]. Exogenous administration of pharmacological doses of TNF-α to experimental animals evokes the pathophysiological events associated with SIRS[48]. In an overwhelming bacterial sepsis model in baboons, passive immunization with a monoclonal antibody to TNF-α before the bacterial challenge confers complete protection against both shock and death. Levels of IL-1β and IL-6 are also attenuated[31]. Passive immunization of mice with anti-TNF-α prevents lethal endotoxaemia[49]. C3H/HeJ mice, which are genetically deficient in the ability to synthesize TNF-α, tolerate lethal doses of endotoxin with minimal effects[50].

Interleukins

IL-1 appears to be released either in parallel or in response to TNF-α secretion[51]. Abrogation of the effects of endotoxin or TNF, by specific antibodies, reduces IL-1 levels and concurrently decreases the mortality rate in experimental animal models. Animal studies in which improvement in survival occurs after blockade of IL-1 activity by use of an IL-1 receptor antagonist (IL-1RA) have provided strong evidence supporting an important role of IL-1 in deleterious effects during Gram-negative bacterial sepsis[52]. Monocytes and tissue macrophages are the primary sources of IL-1. IL-1 consists of two distinct molecules, IL-1α and IL-1β, that are structurally related polypeptides[53]. Most IL-1α remains in the cytosol in a precursor form or is associated with the cell membrane in a biologically active form. The presence of a cell-associated form of IL-1 can explain the capability of activated macrophages to induce natural killer cell cytoxicity, T cell proliferation and other functions by cellular contact in the absence of any releasable IL-1. IL-1β is cleaved by the IL-1β converting enzyme to its mature form within the cell after which it is secreted. IL-1β is also readily degraded from its precursor by trypsin, plasmin and other proteases[51]. There are two classes of high-affinity IL-1 receptors described and tissue distribution varies from 100 to 10000 receptors per cell. Patients with sepsis have greatly enhanced expression of type II IL-1 receptor mRNA and cell surface receptors, and have raised levels of soluble IL-1 receptors which may represent a mechanism of regulating IL-1 activity in sepsis[54]. Both IL-1α and IL-1β have a short half-life of 6–10 min. IL-1α and IL-1β have not been detected in the circulation of human volunteers who received endotoxin intravenously, whereas TNF-α and IL-6 were detected readily[55]. The absence of IL-α during inflammation is consistent with its primary role as a membrane-bound cytokine principally involved in local paracrine and autocrine regulation. IL-1 is a strong inducer of granulocyte/macrophage CSF (GM–CSF), macrophage CSF and hepatic acute-phase protein synthesis. Excessive IL-1 release produces excessive margination of activated neutrophils into the vascular wall, stimulates endothelial cell procoagulant activity and increases leucocyte binding, but decreases heparan sulphate binding[56]. Unlike TNF-α, IL-1 is not directly lethal but IL-1 will reproduce many of the acute haematological and metabolic phenomena associated with severe sepsis and is equipotent in inducing the synthesis of other cytokines[44].

IL-6 is a family of at least six differentially modified phosphoglycoproteins which are released rapidly within 60 min in response to injury[28]. They act as a B cell stimulatory factor, a hybridoma/plasmacytoma growth factor, a hepatocyte stimulating factor and a cytotoxic T cell differentiation factor[57]. The prevailing subtype of IL-6 after an endotoxin challenge is a 26-kDa protein. IL-6 interacts synergistically with IL-1 to affect thymocyte proliferation, and in combination with TNF-α augments T cell proliferation and promotes PMN activation and accumulation. The temporal relationship of IL-6 appearance within the cytokine cascade suggests a strong relationship to antecedent TNF-α or IL-1 stimulation[55]. Transcription and production are enhanced in response to TNF-α and IL-1. When TNF-α or IL-1 activity is attenuated, the subsequent IL-6 response is decreased[58]. IL-6 administration does not cause haemodynamic compromise, regardless of the quantity given. IL-6 suppresses LPS-induced TNF-α production and TNF-α-induced IL-1 production. Anti-IL-6 monoclonal antibodies protect mice from lethal *Escherichia coli* infection and lethal exposure to TNF-α[59].

IL-4 and IL-8 also participate in the response to injury. IL-4 synergistically increases TNF-α or IL-1-induced antigen expression in endothelial cells, but inhibits the increased expression of adhesion molecules by TNF-α, IL-1 or IFN-γ. IL-8 is produced by the endothelial cells and is chemotactic for both neutrophils and lymphocytes. Administration of anti-IL-8 antibodies prevents neutrophil-dependent tissue infiltration and damage[60]. IL-4 enhances lymphocyte adhesion to the endothelial cell. It regulates growth and differentiation of T cells. IL-4 induces antigen expression on macrophages and suppresses IL-8 expression from stimulated monocytes but not from stimulated fibroblasts or endothelial cells.

IFN-γ promotes the release of TNF-α, IL-1 and IL-6 by augmenting the effects of endotoxin on macrophages, thereby increasing the expression of adhesion molecules and cellular receptors for TNF-α. It may act synergistically with TNF-α to produce cytotoxic and cytostatic activity, synergistically increases IL-2 promotion of TNF-α release and promotes B cell activation to increase antibody production. IFN-γ enhances adhesion of lymphocytes to endothelial cells, induces marked morphological changes in endothelial cells, and encourages PMN activation and accumulation. IFN-γ enhances the phagocytic activity of PMNs and macrophage microbial function. IFN-γ antagonizes the actions of GM-CSF. GM-CSF stimulates PMN phagocytosis, degranulation and cytotoxicity. In addition it promotes maturation of macrophages and enhances their activity.

Cells

Endothelium

Because of its position, the endothelium both mediates and modulates the inflammatory and immunological responses in SIRS. The endothelium regulates the microvasculature, reacting to the metabolic needs of the tissue; it is essential in organ autoregulation and in the responses of these microvasculatures to changes in local blood flow through an extensive array of endogenously produced vasoactive factors[61]. The endothelium regulates intravascular coagulation by its participation in and separation of procoagulant pathways, inhibition of procoagulant proteins, regulation of fibrinolysis and production of thromboregulatory compounds[62]. Basal secretion of tissue factor, a procoagulant enzyme, is low compared with that of the underlying smooth muscle cells and fibroblasts. However, if stimulated or injured, the endothelial cells can increase tissue factor production by tenfold to 40-fold. The basic barrier function of the endothelium separates intravascular coagulation factors (Factor VIIa) from tissue factor in the subendothelium and also prevents exposure of platelets to the proaggregating constituents of the subendothelium, such as collagen and von Willebrand factor. Furthermore, endothelial cells produce and express on their extracellular surfaces small amounts of the proteoglycan heparan sulphate, which serves to localize and increase the intrinsic activity of antithrombin III and tissue factor pathway inhibitor where it acts as a potent inhibitor of Factor Xa and, through its interactions with Factor Xa, produces feedback inhibition of the Factor VIIa–tissue factor complex. Endothelial cells inhibit procoagulant proteins with the protein C pathway, an autoregulatory pathway that involves protein C, protein S and thrombomodulin. Besides its direct effects on activated coagulant factors, protein C_a also increases endothelial cell fibrinolytic activity by complexing with and decreasing the activity of PAI-1, thereby increasing fibrinolysis. Endothelial cells synthesize and assemble the plasminogen activators: urokinase (uPA) and tPA. *In vivo*, normal endothelial cells express tPA only. However, if stimulated by a variety of cytokines and circumstances, endothelial cells preferentially synthesize uPA and downregulate tPA synthesis. In addition to these two fibrinolytic enzymes, endothelial cells also secrete two PAIs, PAI-1 and PAI-2. Both are serine protease inhibitors and form equimolar complexes with either active uPA or tPA molecules. PAI-1 requires the presence of fibronectin in the extracellular matrix to maintain its active conformation.

The process of cell adherence, cell activation and cell migration involves an interplay between the expression of adhesion molecules by the endothelial cells, leucocyte activation and local cytokine activity[63]. The adhesion molecules involved in endothelial cell interactions with leucocytes are currently composed of three families: the selectins which govern the interaction of lymphocytes and neutrophils, the immunoglobulins which include antigen-specific receptors for T and B lymphocytes, and the integrins which are important in platelet adhesion and cell migration. The presence of the cytokines IL-1, TNF-α and transforming growth factor (TGF) β or the presence of LPS stimulates endogenous endothelial cell production of IL-1 and IL-6, and induces IL-8 secretion. IL-8 has been shown to regulate transendothelial migration of PMNs through the endothelial barrier. The release of IL-8 is associated with a change in cell adhesion molecule expression from selectins, which are shed into the circulation to integrins which allow firm binding of leucocytes. Moreover, the action of IL-8 is enhanced by the fact that IL-8 is secreted preferentially into the vessel wall and is deposited in the subendothelial matrix by the endothelial cells, giving rise to a transmural chemotactic gradient. When endothelial cells are stimulated by cytokines or thrombin, they express endothelial cell leucocyte adhesion molecule (ELAM) 1 and intercellular adhesion molecule (ICAM) 1. Once activated, endothelial cells also produce an enhancement factor, PAF, which modulates the rapid expression of these adhesion molecules. The selectin, ELAM-1, is expressed on endothelial cells within hours and binds both PMNs and monocytes. The expression of ICAM-1, a member of the immunoglobulin family, is increased by IFN-γ, IL-1 and TNF-α. ICAM-1 facilitates the adhesion of both PMNs and lymphocytes. A second molecule in this series, ICAM-2, which is partly homologous to ICAM-1, mediates the binding of T and B cells to endothelial cells. Vascular cell adhesion molecule (VCAM) 1 is another inducible endothelial surface immunoglobulin which binds both lymphocytes and monocytes. Finally, stimulated endothelial cells can express GMP-140, a surface receptor which preferentially binds platelets. The binding of platelets increases the local availability of PAF and further accelerates the endothelial cell expression of adhesion molecules.

Leucocytes

Neutrophils play a pivotal role in SIRS/sepsis-associated tissue injury. Numerous stimuli can activate neutrophils via specific receptor systems on their surface (TNF-α, IL-1, IL-8, GM-CSF, IFN-γ, leukotriene (LT) B_4, PAF, ICAM-1 and ELAM-1, C3a and C5a). Neutrophils secrete a wide variety of mediators in response to these stimuli, both proinflammatory (IL-1α and IL-1β, TNF-α, IL-6, IL-8, IFN-γ) and anti-inflammatory (TGF-β) cytokines and their antagonists (IL-1RA)[64]. PMN activation is manifested by increased β-2 integrin expression and enhanced superoxide radical generation. Upregulation of C11b correlates with serum IL-6 level[65]. Cell surface nicotinamide adenine dinucleotide phosphate oxidase is activated and large quantities of oxygen metabolites are produced. Lipo-oxygenase and phospholipases produce LTB_4 and PAF which result in further accumulation of neutrophils and enhanced endothelial cell cytotoxicity[66,67]. Neutrophils can degrade elastin and collagen I, II, III and VI, fibrinogen, fibronectin and proteoglycans through the release of a neutral serine protease which is a major component of their granular enzymes. The metalloproteases (MMP-1, MMP-2 and MMP-3) are also secreted and will digest collagen, gelatin and proteoglycans respectively. Neutrophils bear several proteins with antibacterial properties such as BPI, cationic antimicrobial protein and desmins[68]. Neutrophil rolling on the vascular endothelium is regulated in part by the neutrophil cell adhesion molecule L-selectin. In patients with SIRS, neutrophil L-selectin expression is downregulated in a dose- and time-dependent manner by TNF-α[69]. Neutrophils contribute to a procoagulant environment within the microcirculation by activating platelet aggregation and coagulation cascades, and inhibiting fibrinolysis[70,71]. In a porcine model, a monoclonal antibody against E- and L-selectin (EL246) significantly reduces neutrophil accumulation and tissue injury, but does not attenuate deranged pulmonary and systemic haemodynamics[72]. Similarly, organ-specific injury (acute lung injury) can be attenuated by EL246[73].

Circulating monocytes move rapidly along the endothelial cell surface (3–5 l/min for the ascending aorta). The first step in monocyte recruitment is the weak attachment of both monocyte and endothelial cell selectin molecules to their opposing corresponding oligosaccharides. The monocyte selectin, L-selectin, is produced constitutively while endothelial selectin, ELAM-1, is induced by IL-1 and TNF-α. After this initial 'weak' attachment process has been initiated the second step, therefore, be excluded that differences in the postoperative gastrointestinal pH profiles influenced the findings.

It must also be noted that the mean age of control subjects and patients differed. There are conflicting data on the effect of age on pancreatic exocrine function. However, if there is any decline in function with age, this is only marginal.

In conclusion, the results of this study show that preservation of the stomach in PPPD, compared with Whipple's procedure, impairs the synchronous release into the jejunum of ECPMs with solid food, thereby diminishing the efficacy of treatment. Consequently, in the presence of postoperative exocrine pancreatic insufficiency, treatment should be tailored to the procedure. After Whipple's procedure, ECPM treatment is the therapy of choice. Following PPPD, however, ECPM treatment will often be ineffective because the microspheres are retained in the stomach. Whether preparations with a smaller sphere size would give a better result remains to be evaluated. The use of conventional powdered pancreatin enzyme preparations, possibly with additional antisecretory treatment, may give greater efficacy in these patients. In patients on ECPM treatment, addition of an H_2-receptor antagonist or proton pump inhibitor may also improve the efficacy of treatment by preventing dissolution of the ECPMs too distally in the gastrointestinal tract.

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*N-benzoyl-*L*-tyrosyl-*p*-aminobenzoic acid–*p*-aminosalicylic acid test.* *Fig. 3* shows the results of the plasma PABA test (AUC of 6-h plasma PABA concentration) after Whipple's procedure or PPPD, without and during enzyme supplementation. There were no significant differences between patients who had Whipple's procedure (without and during enzyme supplementation), those who had PPPD (without and during enzyme supplementation) and healthy volunteers (ANOVA).

Fig. 4 shows the outcome of the 6-h urinary PABA:PAS ratio after Whipple's procedure or PPPD, without and during enzyme supplementation. The outcome during enzyme supplementation in those who had Whipple's procedure was not significantly different from that in healthy volunteers. In patients who had PPPD, the outcome during enzyme supplementation remained significantly different from that in healthy volunteers ($P<0{\cdot}05$, ANOVA).

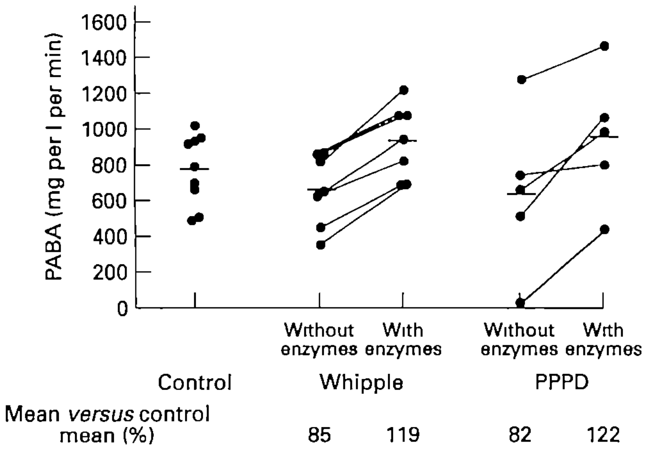

Fig. 3 Results of the plasma *p*-aminobenzoic acid (PABA) test (area under the curve) in nine healthy volunteers (control), in seven patients who had Whipple's procedure and in five who had pylorus-preserving pancreatoduodenectomy (PPPD) without and during enzyme supplementation Horizontal bars represent the mean

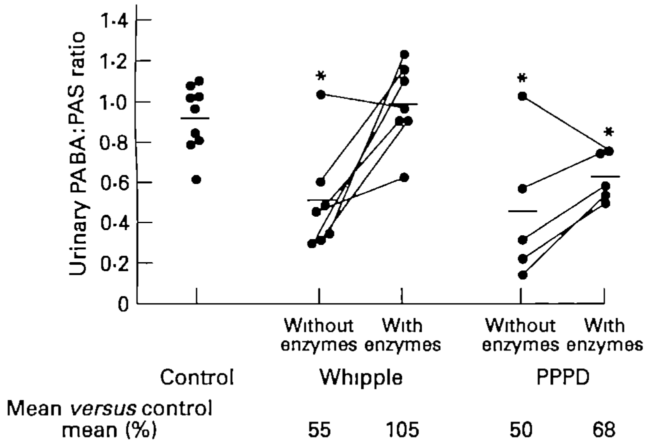

Fig. 4 Results of the urinary *p*-aminobenzoic acid (PABA):*p*-aminosalicylic acid (PAS) ratio in nine healthy volunteers (control), in seven patients who had Whipple's procedure, and in five who had pylorus-preserving pancreatoduodenectomy (PPPD) without and during enzyme supplementation. Horizontal bars represent the mean. *$P<0$ 05 *versus* control (analysis of variance)

Discussion

The present study shows that after Whipple's procedure the gastric transit of ECPMs and food is synchronous and pancreatic enzyme activity is restored to normal levels. but after PPPD gastric transit of ECPMs is much delayed and pancreatic enzyme activity remains well below the normal level.

The essential modification of PPPD compared with Whipple's procedure is preservation of the stomach, which may entail a longer recovery time from delayed gastric emptying in the early postoperative period[18–20]. Whether exocrine pancreatic insufficiency develops after Whipple's procedure or PPPD depends on a number of factors, including the extent of the pancreatic resection, the quality and patency of the pancreatic anastomosis and the condition of the pancreatic remnant. In some patients with cancer of the pancreatic head this is already impaired before operation by fibrosis and atrophy of the parenchyma distal to the obstructing tumour. After pancreatic resection non-optimal stimulation of residual enzyme secretion and non-optimal mixture of enzymes, food and bile may contribute to impaired digestion of nutrients[21].

At present, no reliable data are available with respect to the prevalence of exocrine pancreatic insufficiency after Whipple's procedure or PPPD. If, however, exocrine pancreatic insufficiency has developed after operation, there may be a difference between these procedures with respect to the efficacy of pancreatic enzyme replacement therapy to restore digestive function. Preservation of the stomach has the advantage that the gastric capacity and gastric mixing ability are maintained, which may ensure a better gastric mixture of pancreatic enzymes and food. On the other hand, it may also cause ECPMs to pass through the stomach more slowly than solid food, as was observed in healthy volunteers[10]. In the volunteers, spheres with a diameter greater than 1·7 mm were retained in the stomach, compared with a solid meal.

The present study shows that, in patients who have had Whipple's procedure, the gastric transit time of 2-mm ECPMs is not significantly different from that of a pancake meal. This is in contrast to the results obtained in patients who have had PPPD, in whom the gastric transit of microspheres is much delayed compared with that of the pancake. This difference between the surgical procedures is also reflected in the intraluminal enzyme activity during enzyme supplementation, as measured by indirect pancreatic function test results which, at baseline, were comparable between both groups. During enzyme supplementation in patients who had had Whipple's procedure, results of the cholesteryl $[^{14}\text{C}]$octanoate breath test (reflecting intraluminal carboxyl ester lipase activity), the plasma PABA test (reflecting intraluminal chymotrypsin activity) and the urinary PABA–PAS test (reflecting intraluminal chymotrypsin activity with a correction for possible defects in the absorption or alterations in postabsorptive metabolism of PABA) were similar and not significantly different from those obtained in healthy volunteers. In patients who received enzyme supplementation after PPPD, however, much less improvement was observed, and the outcome of $[^{14}\text{C}]$carbon dioxide recovery in breath and the 6-h urinary PABA:PAS ratio remained well below those of healthy volunteers. Gastrointestinal pH was not measured as this might have interfered with the 'normal' physiology of digestive function in these patients. The possibility cannot, pancake batter together with 1·5 g cholesteryl octanoate. To this batter 15 MBq ^{99m}Tc-labelled albumin colloid was added. The pancake was fried in 10 g butter and spread with jam. Finally, 1000 mg NBT-PABA and 500 mg PAS were sprinkled on to the pancake. The meal contained 1527 kJ (365 kcal) and its calculated waterfree composition was 50 per cent carbohydrate, 37 per cent fat and 13 per cent protein.

Test procedure

Pancreatic enzyme activity was measured on two separate occasions in each patient. First, endogenous pancreatic enzyme activity was assessed. Second, pancreatic enzyme activity during enzyme supplementation was measured. During the latter procedure the gastric transit time of the 2-mm ECPM preparation and the pancake meal was assessed simultaneously. Five days before each test procedure, patients discontinued the use of pancreatic enzyme supplements and drugs that influence gastrointestinal pH (e.g. H_2-receptor antagonists, proton pump inhibitors) and motility (e.g. domperidone).

Participants fasted overnight. Before the test, fasting-state breath and blood samples were obtained for baseline determinations of [^{14}C]carbon dioxide output in breath and of plasma PABA concentration. An untimed urine sample was obtained for baseline urinary PABA and PAS excretion. During dual-isotope image acquisition, patients were seated in an upright position. First, a static image (180 s, frontal view) was obtained after the ingestion of two crushed ^{171}Er-labelled microspheres. This acquisition was used to calculate downscatter from the ^{171}Er channel into the ^{99m}Tc channel. The dynamic image acquisition (frontal view, maximal 130 frames, each of 90 s duration) was then started and patients were fed the pancake meal. Halfway, 50 neutron-activated ECPMs and 60 non-activated microspheres were ingested, without the gelatin capsule in which they are normally contained. Although not formally studied, it is believed that this ensures a better mixture of enzymes and food after antrectomy. For reasons of comparison, the same procedure was used in patients who underwent PPPD. The total enzyme dose was approximately 42 000 units of lipase, 2250 units of proteases and 38 000 units of amylase. Subjects ate the complete pancake. During ingestion of the pancake meal, they also drank 75 ml water. Following the dynamic acquisition, a static image acquisition (300 s, left lateral view) was obtained to visualize the body contour in relation to the position of the stomach and small intestine. This frame was used to compute the regional attenuation. From the start of ingestion of the pancake meal, breath and blood samples were collected at 30-min intervals for 4 h and then hourly for a further 2 h, urine was collected for 6 h. During the first 3 h after the pancake meal, patients were not allowed additional fluids. For 3–6 h, they were encouraged to drink at least 500 ml water or tea. Some 4 h after the pancake meal, they received a standardized light lunch.

Statistical analysis

Results are expressed as mean(s.d.). Data were compared with analysis of variance (ANOVA) (with correction according to Bonferroni for multiple testing) and Wilcoxon matched-pairs signed rank test. To calculate the area under the curve (AUC), for both [^{14}C]carbon dioxide output in breath and plasma PABA concentration, linear interpolation was used. Differences were considered significant when P was less than 0·05 for a two-tailed test.

Results

Gastric transit

Fig. 1 shows the gastric transit of the 2-mm ECPMS and the pancake after Whipple's procedure and after PPPD. After Whipple's procedure, the gastric transit time of the microspheres was 79(59) min and that for the pancake meal was 53(31) min (P not significant, Wilcoxon test). Following PPPD, the transit time of the 2-mm ECPMs was 119(43) min and that of the pancake meal was 50(20) min ($P < 0·05$, Wilcoxon test).

Pancreatic enzyme activity

Cholesteryl [^{14}C]octanoate breath test. *Fig. 2* shows the results of the cholesteryl [^{14}C]octanoate breath test (AUC of 6-h [^{14}C]carbon dioxide output in breath) after Whipple's procedure and after PPPD, without and during enzyme supplementation. After Whipple's procedure, the mean AUC for [^{14}C]carbon dioxide output in breath rose to be no different from that of healthy volunteers. After PPPD, the mean AUC for [^{14}C]carbon dioxide output in breath rose from 15 per cent (without enzyme supplementation) to 57 per cent (during enzyme supplementation) of that of healthy volunteers. Outcome during enzyme supplementation remained significantly different from that in healthy volunteers ($P < 0·05$, ANOVA).

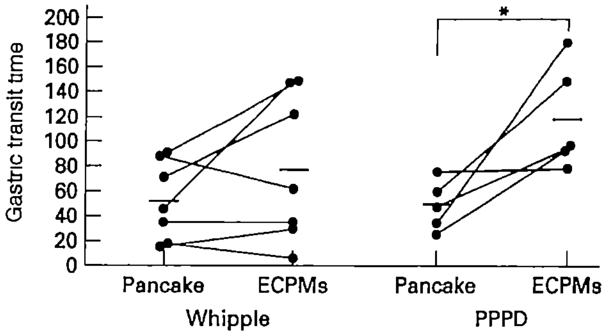

Fig. 1. Gastric transit time of the pancake meal and the enteric-coated pancreatin microspheres (ECPMs) after Whipple's procedure and after pylorus-preserving pancreatoduodenectomy (PPPD). Horizontal bars represent the mean. *$P < 0·05$ (Wilcoxon matched-pairs signed rank test)

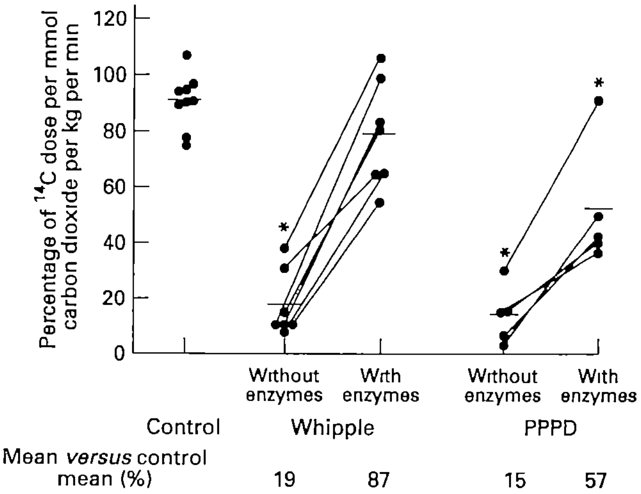

Fig. 2 Results of the cholesteryl [^{14}C]octanoate breath test (area under the curve) in nine healthy volunteers (control), in seven patients who had Whipple's procedure, and in five who had pylorus-preserving pancreatoduodenectomy (PPPD) without and during enzyme supplementation. Horizontal bars represent the mean. *$P < 0·05$ *versus* control (analysis of variance)

observed in healthy volunteers[10]. A comparative study was conducted between patients with exocrine pancreatic insufficiency after Whipple's procedure and after PPPD, to investigate the pharmacodynamics of ECPMs and their gastric transit time in relation to that of a solid meal.

Patients and methods

Experimental design

Patients ingested a solid test meal (pancake) together with 2-mm ECPMs (Panzytrat; Nordmark Arzneimittel, Uetersen, Germany) The gastric transit time of the pancake meal and the microspheres was determined, together with simultaneous assessment of intraluminal pancreatic enzyme activity by two indirect pancreatic function tests. Assessment was also performed without enzyme supplementation to determine endogenous pancreatic enzyme activity.

Patients

The study population consisted of seven patients who had undergone Whipple's procedure and five who had had PPPD. Resections were performed for malignancy of the pancreatic head region and included 80 per cent pancreatectomy with pancreatojejunostomy. All resections were done with curative intent. In two patients, one in each group, total pancreatectomy was performed. At the time of the investigation, no patient was known to have metastatic disease Patients were selected for assessment of endogenous pancreatic function depending on complaints associated with maldigestion and steatorrhoea (abdominal pain, cramping, bloating, diarrhoea, foul-smelling stools) during postoperative follow-up. Patients were included in the study if the result of at least one of the two indirect pancreatic function tests was two standard deviations below the mean value for healthy normals.

The mean(s.d.) age of patients who had Whipple's procedure (six women and one man) was 66(5) years. The mean(s.d.) interval between investigation and surgery was 30(12) months Underlying diseases were pancreatic adenocarcinoma (four patients), distal cholangiocarcinoma (one), villous adenoma of the duodenum (one) and leiomyosarcoma of the duodenum (one). After operation one patient developed insulin-dependent diabetes mellitus.

The mean(s d) age of patients who had PPPD (three women and two men) was 58(10) years The mean interval between investigation and surgery was 12(4) months. Underlying diseases were pancreatic adenocarcinoma (four patients) and ampullary carcinoma (one). After operation two patients developed insulin-dependent diabetes mellitus.

A control group consisted of nine healthy men aged 21–30 years with no history of gastrointestinal, hepatic or renal disease, and with normal findings on physical examination[11]

The study was approved by the medical ethics committee All participants gave written informed consent.

Assessment of gastric transit

Dual-isotope scintigraphy was used to assess the gastric transit profile of the 2-mm ECPM preparation in relation to that of the pancake meal. The pancake meal was labelled by incorporation of ^{99m}Tc-labelled albumin. For labelling the ECPM preparation, a technique involving cold labelling and post-production neutron activation was used. For this, part of the filler compound that was used to produce the ECPMs was replaced by ^{170}Er-enriched erbium oxide (Campro Scientific, Veenendaal, The Netherlands). Each microsphere of this batch contained approximately 0·3 mg ^{170}Er-enriched erbium oxide. Subsequent on-demand post-production neutron activation created the γ-emitting radioisotope ^{171}Er ($t_{1/2} = 7{\cdot}5$ h) and various radiocontaminants. Dosimetric criteria for optimum conditions for neutron activation had been established previously and it had been demonstrated that post-production neutron activation of ^{170}Er-enriched erbium oxide ECPMs could be performed safely within the guidelines set by the World Health Organization for experiments in human volunteers involving radioactive materials[12]

For each experiment, 50 ECPMs were neutron activated 8 h before ingestion, to yield 4 MBq ^{171}Er at the time of ingestion The total committed dose equivalent, resulting from ingestion of the neutron-activated ECPM preparation, did not exceed 0·75 mSv per MBq ^{171}Er, including contributions from all contaminants. The effects of neutron irradiation on enzyme activity, gastric juice resistance and disintegration time of the ECPMs were acceptable, and permitted *in vivo* assessment of small intestinal enzyme activity during gastric transit studies[12]

All acquisitions were performed using a single-headed large-field-of-view camera (Diacam; Siemens, Dusseldorf, Germany) and the factory-standard high-energy collimator. For ^{99m}Tc a 15 per cent window centred at 140 keV and for ^{171}Er a 20 per cent window at 302 keV was used. Acquisitions were performed in dual-isotope mode and 64 × 64 pixel frames (16 bits per pixel) at a rate of one frame per 90 s. Individual frames were corrected for motion, downscatter, decay, background and attenuation Calculation of gastric transit time was performed by means of location–time analysis, resulting in a transit time of the ingested activity quantifying the median delay between entrance into the stomach and passage through the pylorus[13,14]. Gastric transit time indicates the timepoint at which half of the ingested activity (i e. pancake and ECPM) have left the stomach.

Assessment of pancreatic enzyme activity

Cholesteryl [^{14}C]octanoate breath test. The cholesteryl [^{14}C]octanoate breath test is based on the intraluminal hydrolysis of cholesteryl [1-^{14}C]octanoate by cholesterol esterase (carboxyl ester lipase); measurements of [^{14}C]carbon dioxide recovery in breath provide a non-invasive test for ester lipid hydrolysis[11,15]. Cholesteryl octanoate (unlabelled) was purchased from Sigma Chemical (St Louis, Missouri, USA). Cholesteryl [1-^{14}C]octanoate was synthesized at the University of California, San Diego, from [1-^{14}C]octanoic acid (New England Nuclear, Boston, Massachusetts, USA). Breath samples were collected by blowing alveolar air into a solution of 2 ml 96 per cent ethanol and 2 ml hyamine hydroxide 1 mol/l in methanol (Packard, Groningen, The Netherlands). Thymolphthalein (Fluka Chemie, Buchs, Germany) indicator was used to detect completion of saturation of hyamine hydroxide by 2 mmol expired carbon dioxide. [^{14}C]carbon dioxide output in breath was measured by liquid scintillation counting. Results were expressed as the percentage of administered radioactivity (^{14}C) excreted per millimole of carbon dioxide after correction for body-weight.

N*-benzoyl-*L*-tyrosyl-*p*-aminobenzoic acid–*p*-aminosalicylic acid test* This test is based on the intraluminal hydrolysis of the peptide *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid (NBT-PABA) by pancreatic chymotrypsin, measurement of plasma PABA concentrations or urinary PABA recovery provided an indirect test for protein digestion[11,16]. Calculation of the PABA:*p*-aminosalicylic acid (PAS) ratio corrects for possible defects in the absorption or alterations in postabsorptive metabolism of PABA[17]. NBT-PABA (sodium salt) was purchased from Fluka Chemie. PAS was purchased from Sigma Chemical. Concentrations of PABA in plasma (mg/l) were determined by high-performance liquid chromatography (HPLC), as were the concentrations of PABA and PAS in urine. Cumulative 6-h urinary recovery of PABA and PAS was expressed as the percentage of the amount of substrate recovered in the 6-h urine collection compared with the total amount administered orally. HPLC assays of PABA and PAS were performed as described elsewhere[11].

Test meal

The test meal consisted of a pancake made from 100 ml whole milk, 50 g flour and 25 g beaten egg. Cholesteryl [^{14}C]octanoate (5 μCi dissolved in 0·2 ml *n*-hexane) was mixed carefully into the

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Comparative effects of enteric-coated pancreatin microsphere therapy after conventional and pylorus-preserving pancreatoduodenectomy

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Background A comparative study was performed between patients with exocrine pancreatic insufficiency after conventional pancreatoduodenectomy (Whipple's procedure) and pylorus-preserving pancreatoduodenectomy (PPPD). In these patients the pharmacodynamics of 2-mm enteric-coated pancreatin microspheres (ECPMs) and their gastric transit time in relation to that of a solid meal were investigated. The efficacy of ECPM preparations may differ after Whipple's procedure compared with PPPD, because the latter procedure does not include gastrectomy.

Methods Gastric transit was assessed by double-isotope scintigraphy. A pancake meal was labelled with ^{99m}Tc. ECPMs were cold-labelled with ^{170}Er and neutron activated shortly before ingestion to enable imaging with a γ camera. Intraluminal pancreatic enzyme activity was assessed during a 6-h period with two indirect tests: the cholesteryl [^{14}C]octanoate breath test and the *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid–*p*-aminosalicylic acid (NBT-PABA–PAS) test.

Results In patients who had Whipple's procedure, the gastric transit time of ECPMs and of the pancake meal was not significantly different. The outcome of the indirect pancreatic function tests during enzyme supplementation was comparable, and not significantly different, from that in healthy volunteers. In patients who had PPPD, however, the gastric transit time of microspheres was greatly delayed compared with that of the pancake meal ($P < 0·05$). Improvement in the outcome of the indirect pancreatic function tests during enzyme supplementation was much less and remained well below that of healthy volunteers ($P < 0·05$).

Conclusion In cases of exocrine pancreatic insufficiency after Whipple's procedure, 2-mm ECPM treatment adequately restores pancreatic enzyme activity. Following PPPD, however, ECPM treatment is often ineffective because the microspheres are retained in the stomach. In these patients, use of conventional powdered pancreatin enzyme preparations may improve the efficacy of treatment.

The prevalence of exocrine pancreatic insufficiency after pancreatic resection varies widely according to the type and extent of surgery, the selection of patients and the criteria set to define malabsorption[1–5]. Theoretically, it includes decreased activity of amylase, trypsin and lipase, producing carbohydrate, protein and fat maldigestion. In clinical practice, however, impaired digestion of fat is the key problem and the most difficult to abolish.

Exocrine pancreatic insufficiency has traditionally been treated with conventional (non-enteric-coated) pancreatin preparations. At present, enteric-coated pancreatin microsphere (ECPM) preparations are used with increasing frequency. These preparations consist of multiple pancreatin microspheres coated with a pH-sensitive polyacrylic acid surface. This layer dissolves if the gastrointestinal pH rises above a threshold (commonly 5·0–5·5) and offers partial protection against the fast and irreversible acidic inactivation of lipase (pH less than 4·0). Indications for postoperative pancreatic enzyme replacement therapy are determined by the consequences of exocrine pancreatic insufficiency: failure to maintain or regain body-weight due to high faecal caloric losses, and symptoms related to steatorrhoea such as frequent, loose and foul-smelling fatty stools, and abdominal cramps.

The classical conventional one-stage pancreatoduodenectomy includes cholecystectomy, resection of the distal common bile duct, duodenectomy, resection of the distal stomach, and excision of the pancreatic head and peripancreatic lymph nodes[6,7]. Reconstruction includes pancreatojejunostomy, hepatojejunostomy and gastroenterostomy. A major modification of Whipple's procedure was introduction of pylorus-preserving pancreatoduodenectomy (PPPD)[8,9]. The principal difference is the preservation of the stomach and 2 cm of the proximal duodenum and reconstruction by end-to-side duodenojejunostomy. Because of this, the efficacy of ECPM therapy after Whipple's procedure may differ from that following PPPD. The latter procedure has the advantage of preserving gastric capacity and gastric mixing ability, which may improve mixture of pancreatic enzymes and food. On the other hand, preservation of the stomach and pyloric function may also cause dys-synchronization in the gastric transit of microspheres and food, as was

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Discussion

Tumours of the ampulla of Vater are rare. During the study period 23 patients were treated for an ampullary adenoma, while 67 patients were treated for an ampullary carcinoma in this hospital during the same time[11]. The treatment strategy for adenoma of the ampulla is based on case reports and small retrospective studies. This study is one of the largest single reports of this lesion.

The present results demonstrate that preoperative diagnosis and staging of ampullary adenomas is unreliable. The diagnosis of infiltrating adenocarcinoma was missed in one-third of the patients using endoscopic biopsy. This is in accordance with previous studies, reporting that malignancies were not identified in 25–56 per cent of cases[1,12]. Focal areas of malignancy may be present in an adenoma and small biopsies obtained endoscopically may not be representative of the entire lesion. Therefore, areas of malignant change can be missed, as illustrated by this experience.

Staging of carcinoma of the ampulla by endoscopic ultrasonography has a reported accuracy of 80–90 per cent[7,13]. Endoscopic ultrasonography has been advocated as the standard diagnostic procedure to identify superficial tumours (adenomas and intramucosal carcinomas) suitable for local resection[5]. In this study, endosonography did not identify invasion in the four patients with invasive carcinoma, whereas the overall accuracy in assessing malignant invasion was only 44 per cent. Also, a false-positive outcome for metastatic lymph nodes was noted in five of 16 cases. Although endoscopic ultrasonography is used successfully for preoperative staging of ampullary carcinomas, in the authors' hands it was not useful in selecting therapy for adenomas. A possible explanation is that carcinomas are more hypoechogenic, which makes them more visible on endoscopic ultrasonography.

All but one patient suspected of malignancy by endoscopic ultrasonography were treated by a Whipple procedure. In retrospect endoscopic ultrasonography results were a major influence on the treatment, as other criteria including age, surgical risk, tumour size and degree of dysplasia were equally distributed between the two treatment groups The present results do not support this reliance on staging of adenomas by endoscopic ultrasonography.

In this study pancreaticoduodenectomy was associated with more complications and a longer hospital stay than local resection. The mortality rate of 9 per cent (one of 11 patients) after pancreatectomy is relatively high and influenced by the limited number of patients During the past decade the mortality rate after pancreatic resection has decreased to less than 5 per cent in this and other specialized centres[14]. In the authors' past 75 Whipple procedures the mortality rate was 2 per cent[15,16].

After local resection, margins were free from tumour in only half of the patients. Furthermore, none of the infiltrating carcinomas was resected radically by local resection. Surprisingly, the recurrence rate was lower than expected; only two patients had tumour recurrence. Recent retrospective reviews have reported similar long-term survival after local resection[17,18]. This may be a result of the improved technique of local resection. A more extensive local resection, including the papilla and adjacent duodenal and ductal tissue, is possible[8,9]. Moreover, additional treatment was performed when a malignancy was diagnosed after operation, which probably reduced the recurrence rate.

In conclusion, this study emphasizes the role of local resection of ampullary tumours. With low morbidity and mortality rates and good long-term results, local resection is certainly an adequate treatment for patients with ampullary adenoma. Unfortunately, an accurate differentiation between benign and malignant tumours is difficult before surgery. Biopsies and endoscopic ultrasonography are unreliable. Furthermore, frozen sections obtained during surgery cannot be relied upon to exclude malignancy[17]. However, when malignancy is diagnosed after operation, a pancreatectomy or other additional treatments (i.e. endoscopic laser/diathermic treatment or radiotherapy) are always an option.

Therefore pancreaticoduodenectomy remains the treatment of choice for ampullary adenoma in patients in good general condition. In elderly and high-risk patients local resection seems an adequate alternative treatment.

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Results

In the study period 35 patients were diagnosed histologically with an ampullary adenoma. Nine patients were excluded because they were treated elsewhere. Three patients were not treated surgically because of concomitant disease and/or poor life expectancy owing to other causes. As a result 23 patients were included in this study, 14 men and nine women, with a median age of 68 (range 29–78) years. The most common presenting symptoms were obstructive jaundice (11 patients), abdominal pain (nine), weight loss (ten) and fatigue (seven). Endoscopic ultrasonography was used for local staging in 18 patients. The preoperative histological diagnosis and estimates of dysplasia are listed in *Table 1*.

Eleven patients underwent a pancreaticoduodenectomy (including two patients who had a pylorus-preserving operation) and 12 patients had a local resection. No statistically significant differences were observed between the two treatment groups concerning age, degree of dysplasia and surgical risk, as summarized in *Table 1*.

Postoperative complications are listed in *Table 2*. One patient died from sepsis, caused by leakage, 7 days after pancreaticoduodenectomy. After pancreatectomy, four patients required relaparotomy compared with two after local resection. One of these patients had incomplete resection of an adenocarcinoma and local resection was therefore converted to a Whipple procedure. The mean duration of hospital stay differed significantly: 36 days for pancreaticoduodenectomy and 18 days for local resection ($P = 0{\cdot}001$). Late complications were observed in six patients after pancreaticoduodenectomy (most frequently diabetes mellitus) and in only one patient after local resection.

Postoperative pathological findings (*Table 3*) showed a median tumour diameter of 1·5 (range 0·5–5·5) cm. There was no statistically significant difference in tumour size between the two treatment groups. Twenty-one patients had ampullary tumours and two tumours were primarily located in the duodenum. Infiltrating adenocarcinoma was present in seven patients; one submucosal carcinoma (T_1) and six carcinomas infiltrating the muscularis propria (T_2). None of these patients appeared to have lymph node involvement; four were treated by local resection.

Pancreaticoduodenectomy was radical in all patients. After local resection the resection was incomplete in six patients (three adenomas and three T_2 carcinomas). Four patients received additional treatment: Whipple procedure ($n = 1$) or radiotherapy ($n = 1$) for infiltrating carcinoma, and destruction with a diathermy snare ($n = 1$) or laser treatment ($n = 1$) for adenoma.

Table 1 Demographic data, histological diagnosis and operative risk of 23 patients treated by pancreaticoduodenectomy or local resection for adenoma of the ampulla of Vater

	Pancreaticoduodenectomy ($n = 11$)	Local resection ($n = 12$)
Sex ratio (M:F)	6:5	8:4
Median age (years)	68	65
Histology		
Villous adenoma	4	3
Slight dysplasia	0	2
Moderate dysplasia	3	1
Severe dysplasia	4	6
Surgical risk		
ASA I	3	1
ASA II	5	7
ASA III	3	3
ASA IV	0	1

ASA, American Society of Anesthesiologists

Of the 18 patients who underwent preoperative endoscopic ultrasonography, four had invasive adenocarcinoma (one T_1 submucosal tumour and three T_2 tumours). Depth of invasion was described in 16 cases and malignant invasion was not identified in any patient ($n = 4$) with invasive carcinoma. Furthermore, endoscopic ultrasonography was false positive for invasion in five patients and false positive for lymph node metastasis in five patients.

The mean duration of follow-up of the 22 patients was 43 (range 1–78) months after pancreaticoduodenectomy, and 36 (range 5–105) months after local resection. Three patients died during the follow-up period (two after local resection and one after pancreaticoduodenectomy). One patient probably died from tumour recurrence, 15 months after a non-radical local resection of an adenoma. Although the cause of death is unknown, a tumour-related death was suspected because of severe cachexia and development of diabetes. Two patients died from other unrelated causes, 7 months after non-radical local resection of a carcinoma and 6 years after pancreaticoduodenectomy. In the remaining 19 patients (ten who had local resection and nine pancreatectomy) one local recurrence was observed at follow-up biopsy. Villous adenoma was still present 5 months after non-radical resection of an adenoma with no additional treatment.

Table 2 Results of surgical treatment of 23 patients diagnosed with adenoma of the ampulla of Vater

	Pancreaticoduodenectomy ($n = 11$)	Local resection ($n = 12$)
Mean (range) hospital stay (days)	36 (20–60)	18 (9–32)*
Operative death	1	0
Operative complications	7 (64)	3 (25)
Haemorrhage	1	2
Leakage/infection	3	1
Subphrenic abscess	1	0
Wound abscess	1	0
Cardiac failure	1	0
Relaparotomy	4	2
Late complications	6 (55)	1 (8)
Diabetes mellitus	4	0
Exocrine insufficiency	1	0
Ileus	1	0
Pancreatitis	0	1

Values in parentheses are percentages. *$P < 0{\cdot}001$

Table 3 Postoperative histological findings of 23 patients diagnosed with a villous adenoma of the ampulla of Vater

	Whipple procedure ($n = 11$)	Local resection ($n = 12$)
Villous adenoma	5	8
T_1 carcinoma (mucosa)	3	0
T_1 carcinoma (submucosa)	0	1
T_2 carcinoma (muscularis propria)	3	3

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Local resection or pancreaticoduodenectomy for villous adenoma of the ampulla of Vater diagnosed before operation

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Background Treatment of ampullary adenoma is complicated by difficult preoperative staging, malignant potential and a high recurrence rate. This study was designed to assess the accuracy of diagnosis and staging by endoscopic biopsy and endosonography, and to compare the results of local resection and pancreaticoduodenectomy (Whipple procedure).

Methods All 23 patients, diagnosed by endoscopic biopsy and surgically treated by local resection ($n = 12$) or pancreaticoduodenectomy ($n = 11$) between 1984 and 1994, were analysed retrospectively.

Results Pancreaticoduodenectomy was associated with more complications (seven of 11 patients *versus* three of 12) and a longer hospital stay (36 *versus* 18 days) than local resection. After local resection tumour excision was incomplete in half of the patients. One patient died after a Whipple procedure. Endoscopic biopsy did not identify infiltrating carcinoma in seven of the 23 patients. Endoscopic ultrasonography had a 44 per cent accuracy rate for tumour invasion and was false positive for lymph node metastases in five of 16 patients. After local resection one recurrence was observed during follow-up and one possibly died from tumour recurrence.

Conclusion Diagnosis and staging of ampullary adenomas by endoscopic biopsy and endosonography was unreliable. Local resection seems a viable alternative for patients whose general condition does not allow a Whipple procedure.

Villous adenoma of the ampulla of Vater is rare, with a reported incidence of 0·04–0·12 per cent[1,2]. The adenoma–carcinoma sequence is generally accepted for these tumours. Hence, management is complicated by a high incidence of malignancy[3,4]. Moreover, preoperative diagnosis is difficult because endoscopic biopsies are often not representative of the entire lesion and malignancy may be missed without complete excision. The value of ultrasonography and computed tomography is limited in excluding malignancy. Endoscopic ultrasonography seems to be accurate in staging ampullary carcinomas according to the tumour node metastasis (TNM) system[5,6]. A recent report suggests that it may be helpful in selecting treatment for ampullary adenomas as well[7].

Although complete excision of these tumours is mandatory, the procedure of choice remains controversial. The two surgical options are local resection or a (pylorus-preserving) Whipple procedure (pancreaticoduodenectomy). A Whipple procedure leads to radical excision and is an adequate treatment, in particular if a carcinoma is diagnosed after operation. Local resection is a more limited procedure, probably associated with less complications. Nevertheless it is usually offered only to elderly patients in poor general condition, because it is associated with a high recurrence rate[1].

The aim of this study was to assess the accuracy of preoperative diagnosis and staging by endoscopic biopsy and endoscopic ultrasonography, and to compare the results of local resection and pancreaticoduodenectomy.

Patients and methods

The database of the Department of Pathology was searched for all patients with a histological diagnosis of ampullary (tubulo)villous adenoma, diagnosed by endoscopic biopsy from 1984 to 1994. Records were reviewed and all patients who underwent subsequent surgical treatment in this institution were included in the study.

Preoperative endoscopic ultrasonography was performed with Olympus GF-UM2, GF-UM3 or GF-UM20 endoscopes (Olympus Optical, Tokyo, Japan) at frequencies of 7·5 and/or 12 MHz. It was performed by one of two experienced operators.

All patients underwent pancreaticoduodenectomy or local resection. Selection for the procedure was according to the surgeon's preference. Local resection consisted of a wide resection of the papilla of Vater, encompassing a part of the posterior duodenal wall and the distal end of the biliary and pancreatic ducts and reimplantation of both ducts in the dorsal duodenal wall as described previously[8,9].

The results of the operative procedures were compared with respect to morbidity and mortality rates, and duration of hospital stay. When additional treatment was necessary after local resection of a carcinoma, the additional days in hospital were included in the duration of hospital stay.

Carcinomas were staged according to the TNM classification[10]. Endoscopic ultrasonography results and final pathological findings were compared regarding presence and depth of infiltration of carcinoma (T stage), and the presence or absence of regional lymph node metastases (N stage).

Recurrence and survival was recorded by follow-up information from visits to the outpatient clinic The most recent information was obtained through telephone contact with the referring physician. In addition, endoscopy and biopsy were performed on patients treated by local resection, to exclude recurrent ampullary tumours

The Mann–Whitney U test was used for statistical comparisons and P values less than 0·05 were considered to be significant

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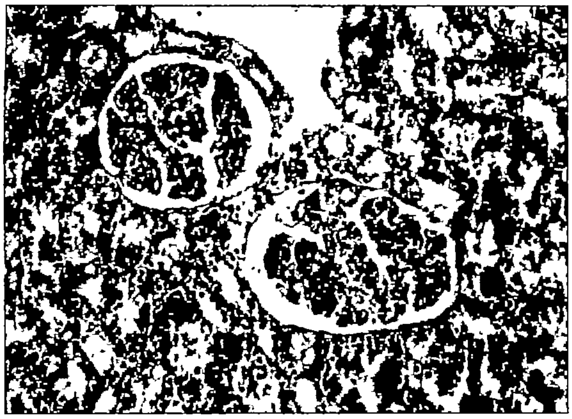

Fig. 5 Light microscopic section from bile duct-ligated rat kidney showing normal glomerular structure with bile pigment accumulation within the tubules and significant congestion of the vascular bed (Haematoxylin and eosin stain, original magnification × 230)

Discussion

The pathological changes found within the kidney following the development of renal failure associated with obstructive jaundice are quite non-specific and vary from minimal changes to acute tubular necrosis, with glomerular and peritubular fibrin deposition[13]. In this study, no glomerular or tubular damage could be demonstrated in the bile duct-ligated rats with the exception of significant venous dilatation and congestion throughout the vascular bed. Furthermore, bile pigment accumulations were seen in the cortex of the kidney, especially in the proximal tubules.

Despite the intense clinical and investigative interest, the exact aetiology of renal dysfunction in patients with obstructive jaundice remains elusive. There has been increasing evidence that gut-derived endotoxins are the prime cause of renal dysfunction in patients with biliary obstruction[18,25]. In obstructive jaundice, increased absorption of endotoxins[25], together with impaired hepatic clearance account for endotoxaemia[26–29] which is associated with both functional renal failure and acute tubular necrosis[19]. In the present study, there was a correlation between endotoxaemia, bilirubin level and renal dysfunction. Bilirubin levels were increased and creatinine clearance was decreased significantly in the bile duct-ligated endotoxin-positive rats.

Although the bile ducts were doubly ligated and then divided to prevent recanalization, endotoxaemia could not be demonstrated in six of the 27 bile duct-ligated rats. Although the mean(s.e.m.) plasma bilirubin level (2·9(1·2) mg/dl) was above the normal range, this rise was modest when compared with that in the endotoxin-positive group. This modest rise in plasma bilirubin level could be secondary to the formation of spontaneous internal drainage in the group of rats that were found to be endotoxin negative and were excluded from the study.

Basal perfusion pressure of the isolated perfused kidneys from bile duct-ligated rats was lower than that in the control and sham-operated animals. This group of rats also had histological evidence of renal vascular dilatation and congestion. These results suggest that there is significant dilatation in the renal vascular bed of jaundiced rats. However, in 1970 Epstein *et al.*[30] suggested that in obstructive jaundice and hepatorenal syndrome, renal hypoperfusion due to active vasoconstriction of renal vascular bed was the cause of renal failure[30]. On the other hand, the decreased blood pressure and reduced systemic vascular resistance in hepatorenal syndrome suggest the likelihood of excess production of a vasodilator[15] and recent attention has focused on nitric oxide as a mediator[22].

In the present study nitric oxide-mediated vasodilatation of the renal vascular bed was evaluated in experimental jaundiced rats. In bile duct-ligated rats the vasodilatory responses induced by acetylcholine were significantly attenuated when compared with those in the other groups. This finding confirms the results of previous studies in which endotoxaemia produced exogenously resulted in loss of acetylcholine-induced endothelium-dependent relaxation in several vascular beds[31–33]. Exogenously administered endotoxin (4–5 mg/kg intravenously or intraperitoneally) has been shown in experimental animals to produce endothelial damage while sparing endothelium-independent guanosine 3′, 5′-cyclic monophosphate (cGMP)-mediated vasorelaxation. However, in the present study the endothelium-independent cGMP-mediated vasorelaxation to nitroglycerine was also significantly attenuated in the bile duct-ligated group. This difference may be explained by use of different experimental endotoxaemia models. In the present model, endotoxins were not given exogenously; they are probably gut derived as bile duct ligation results in endogenous endotoxaemia.

Endotoxin or cytokines lead to the induction of nitric oxide synthase in both endothelium and smooth muscle and to progressive vascular relaxation. Once induced, the enzyme releases nitric oxide for many hours without further stimulation[34]. Therefore a high nitric oxide concentration in both endothelium and smooth muscle cells may lead to overproduction of cGMP which results in desensitization to endogenous and exogenous nitrates that produce vasodilatation by cGMP. This may explain the loss of endothelium-dependent and independent cGMP-mediated vasodilator responses in the present model. Similarly Waldman *et al.*[35] have suggested that the development of tolerance to nitrovasodilators is due to impaired metabolism of nitric oxide and desensitization of soluble guanylate cyclase to nitric oxide[35]. The present results with forskolin, the endothelium-independent adenosine 3′, 5′-cyclic monophosphate-mediated vasodilator[36] also confirm this hypothesis. No significant difference was found in the relaxation response to forskolin in the bile duct-ligated group compared with the control group.

In conclusion, it is suggested that endogenous endotoxaemia in obstructive jaundice may lead to the induction of nitric oxide synthase and to progressive vascular relaxation in the renal vascular bed. The overproduction of nitric oxide may cause endothelial damage and/or desensitization of guanylate cyclase which in turn may result in loss of endothelium-dependent and -independent cGMP-mediated vasorelaxation. Therefore the disruption of renal vascular tone and haemodynamic regulation may be the cause of hypoperfusion and renal dysfunction in obstructive jaundice. These findings support the beneficial effect of early intervention in obstructive jaundice to prevent detrimental changes in the kidney. Blockage of nitric oxide production may reverse some of these effects and may be considered in the future management of patients with obstructive jaundice.

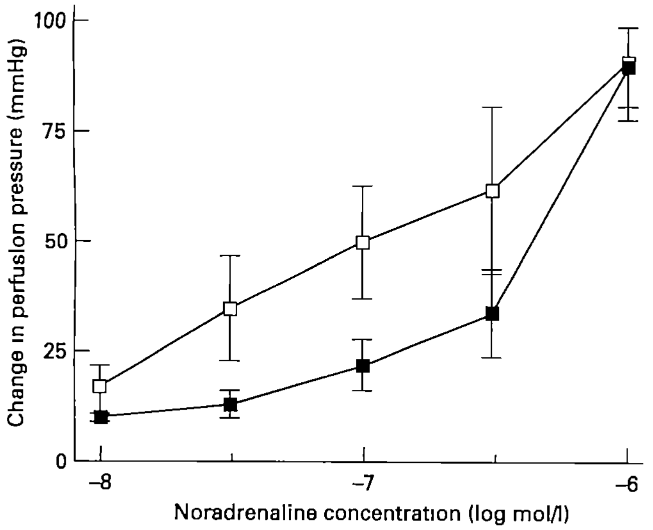

Fig. 1 Mean(s.e.m.) changes from base line in perfusion pressure induced by noradrenaline in isolated perfused rat kidney from bile duct-ligated (■; $n=5$) and control (□; $n=5$) groups

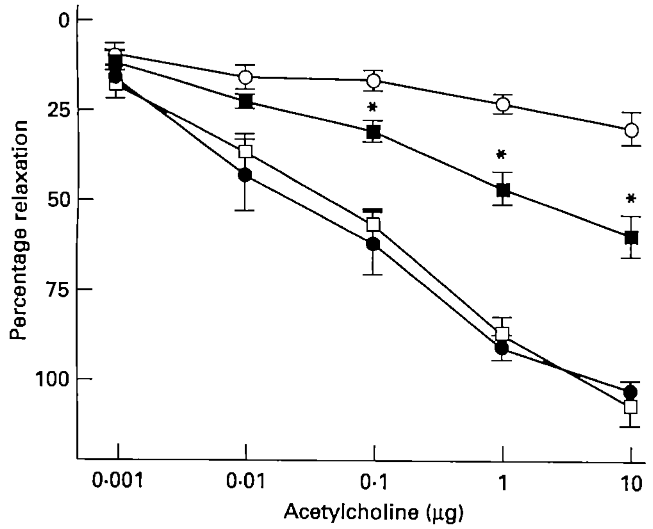

Fig. 2 Vasodilatory response to acetylcholine expressed as mean(s.e.m.) percentage of the observed response to noradrenaline in isolated perfused kidney from control rats in the absence (□; $n=9$) and presence (○; $n=5$) of *N*-nitro-L-arginine methyl ester 3×10^{-5} mol/l, and from sham-operated (●; $n=6$) and bile duct-ligated (■; $n=6$) rats. $^*P<0\cdot02$ *versus* control and sham groups (Mann–Whitney *U* test)

($n=6$) but was not changed in the sham-operated group ($n=6$) compared with the control response ($n=9$) (*Fig. 2*).

Endothelium-independent vasodilators nitroglycerine and forskolin were also tested at the raised tone. Nitroglycerine and forskolin (0·001–10 µg) decreased the perfusion pressure in a concentration-dependent manner (*Figs 3* and *4*). The vasodilator effect of nitroglycerine was significantly attenuated in the bile duct-ligated group ($n=5$) ($P<0\cdot02$) compared with the control group ($n=5$). However, the response to forskolin was not altered by ligation of the bile duct ($n=5$).

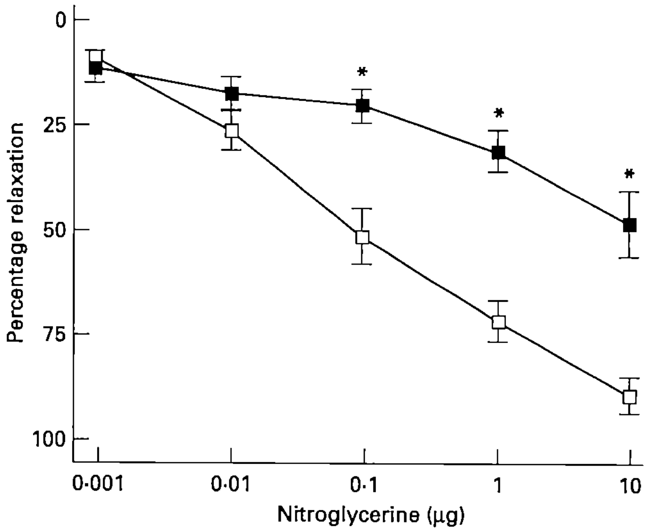

Fig. 3 Vasodilatory response to nitroglycerine in isolated perfused rat kidney from control (□; $n=5$) and bile duct-ligated (■; $n=5$) groups. Data are expressed as mean(s.e.m.) percentage of the observed response to noradrenaline. $^*P<0\cdot02$ *versus* controls (Mann–Whitney *U* test)

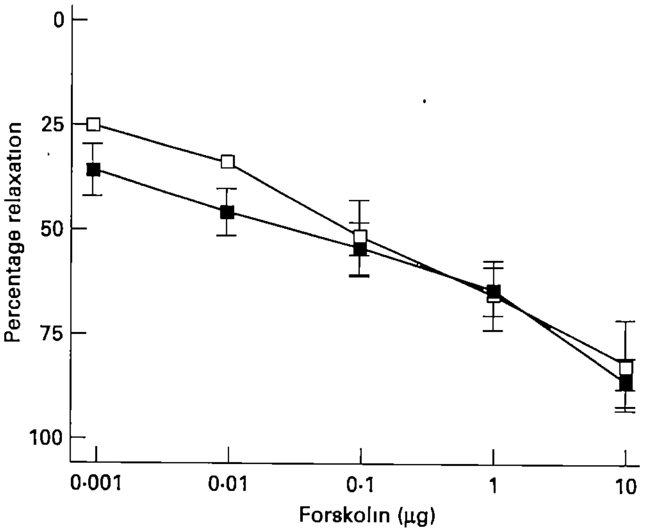

Fig. 4 Vasodilatory response to forskolin in isolated perfused rat kidney from control (□; $n=5$) and bile duct-ligated (■; $n=5$) groups. Data are expressed as mean(s.e.m.) percentage of the observed response to noradrenaline

Histological examination

Light microscopic examination of kidney showed that there was significant venous dilatation and congestion in the vascular bed of the bile duct-ligated group. Bile pigment accumulations were seen in the cortex of the kidney especially in the proximal tubules. There was no glomerular or tubular damage (*Fig. 5*). Bile duct proliferation, sinusoidal, vascular dilatation and congestion without fibrosis were revealed by microscopic examination of the liver. Also there was feathery necrosis in the parenchyma of the liver. Histological examination of kidney and liver did not show any pathological changes in the sham and control groups.

meantime, 2 ml blood was collected from the inferior vena cava and the right kidney with the left lobe of the liver were resected for microscopic evaluation. Perfusion of the isolated left kidney was carried out continuously with oxygenated (95 per cent oxygen and 5 per cent carbon dioxide) and warmed (37°C) Krebs–Henseleit solution (KHS), using a Harvard peristaltic pump (model 1203a) (Newport Beach, California, USA) at a constant flow of 0·025 ml per g per min. KHS had the following composition: NaCl 95 mmol/l, KCl 4·7 mmol/l, $MgSO_4$ 1·2 mmol/l, $CaCl_2$ 2·5 mmol/l, KH_2PO_4 1·2 mmol/l, $NaHCO_3$ 25·0 mmol/l and glucose 11·1 mmol/l. Indomethacin 10^{-5} mol/l was also added to the perfusion medium. Mean perfusion pressure was measured via a pressure transducer and monitored continuously on a computer by 'transducer data acquisition system (MAY 95)' (Commat, Ankara, Turkey).

Experimental protocol

At the flow rate used, the perfusion pressure stabilized within 30 min. Some kidneys in which the initial perfusion pressure increased progressively and tissue oedema occurred were excluded from the study ($n = 7$). Each kidney preparation was used to study only one of the following parameters.

Pressor responses to noradrenaline. The pressor response was determined in isolated perfused kidneys from the control and bile duct-ligated group of rats. Noradrenaline at 10^{-8}–10^{-6} mol/l was added into the perfusion reservoir in a cumulative manner.

Endothelium-dependent relaxation responses to acetylcholine. The endothelium-dependent vasodilatory effect of acetylcholine was evaluated in isolated perfused rat kidneys from control, sham and bile duct-ligated groups of rats. Perfusion pressure was increased to 80 per cent of the maximum pressor response elicited by noradrenaline (3×10^{-7} mol/l). Then, increasing concentrations of acetylcholine (0·001–10 µg) were applied by single injections in a volume of 0·01 ml, through a rubber tubing segment distal to the perfusion pump. The involvement of nitric oxide in the acetylcholine-induced vasodilator response was also tested. For this purpose *N*-nitro-L-arginine methyl ester (L-NAME) 3×10^{-5} mol/l was added to the perfusion reservoir and the response to acetylcholine was re-evaluated in the control group.

Endothelium-independent relaxation responses to nitroglycerine and forskolin The endothelium-independent vasodilator effect of nitroglycerine and forskolin was evaluated in isolated perfused rat kidney from control and bile duct-ligated groups of rats. Perfusion pressure was increased to 80 per cent of the maximal pressor response elicited by noradrenaline (3×10^{-7} mol/l). Then, increasing concentrations of nitroglycerine and forskolin (0·001–10 µg) were applied as described for acetylcholine

Histological and biochemical evaluation

Specimens of renal and hepatic tissue from bile duct-ligated, sham and control rats were stained with haematoxylin and eosin, silver and trichrome for histological examination. Orsein and Prussian histochemical stains were used also to evaluate the nature of the pigments.

Plasma bilirubin and creatinine, and urine creatinine levels were measured in each group of rats. Hyperbilirubinaemia was defined as a plasma total bilirubin concentration higher than 1·2 mg/dl. Creatinine clearance rates were calculated by the use of standard formulae. Plasma endotoxin was determined using *Limulus* amoebocyte lysate (E-Toxate). The reaction was interpreted as positive if a solid gel was formed or negative if no gel was formed.

Reagents

Acetylcholine, noradrenaline, nitroglycerine, *Limulus* amoebocyte lysate (E-Toxate), indomethacin, forskolin, L-NAME and urethane were from Sigma (St Louis, Missouri, USA).

Statistical analysis

Responses to acetylcholine, nitroglycerine and forskolin are expressed as a percentage of the noradrenaline-induced pressor response. Statistical analysis was performed using the Mann–Whitney *U* test for unpaired comparisons. $P < 0.05$ was considered significant.

Results

Endotoxin

When the presence of endotoxin was determined in the plasma, the *Limulus* lysate assay gave positive results in 21 of the 27 bile duct-ligated rats. Rats that had undergone bile duct ligation but were found to be endotoxin negative ($n = 6$) were excluded from the study. Rats in the control and sham groups were all endotoxin negative.

Biochemical analysis

The mean(s.e.m.) plasma bilirubin level of the bile duct-ligated group was 7·80(0·39) mg/dl ($n = 21$) and was significantly higher than that in the sham ($n = 6$) and control ($n = 6$) groups (*Table 1*). Creatinine clearance was significantly reduced in the bile duct-ligated group (mean(s.e.m.) 0·21(0·04) ml/min) ($n = 21$) compared with that in the other groups (*Table 1*).

Renal vascular bed responses

In isolated rat kidneys mean(s.e.m.) baseline renal perfusion pressure was 68·7(5·9) mmHg in the control group ($n = 24$). Perfusion pressure in the sham-operated ($n = 6$) group was 68·7(12·0) mmHg and was not significantly different from that in the control group. However, basal perfusion pressure of the bile duct-ligated group was 23·8(1·5) mmHg ($n = 21$) and was significantly lower ($P < 0.02$) than that in the other groups.

Perfusion pressure of the isolated perfused rat kidneys from control ($n = 5$) and bile duct-ligated ($n = 5$) groups was increased by the administration of increasing concentrations of noradrenaline (10^{-8}–10^{-6} mol/l). Pressor responses to noradrenaline were not significantly different between groups (*Fig. 1*).

Administration of acetylcholine (0·001–10 µg) at the raised tone produced a concentration-dependent decrease in perfusion pressure in the control group. This vasodilatory response was mediated by acetylcholine-induced release of nitric oxide since it was inhibited in the presence of L-NAME 3×10^{-5} mol/l ($n = 5$). Acetylcholine-induced vasodilatation was found to be significantly attenuated by bile duct ligation ($P < 0.02$)

Table 1 Total bilirubin levels and creatinine clearance in jaundiced and control rats

Group	Total bilirubin (mg/dl)	Creatinine clearance (ml/min)
Bile duct-ligated ($n = 21$)	7·80(0·39)*	0·21(0·04)*
Sham ($n = 6$)	0·46(0·01)	0·45(0·03)
Control ($n = 6$)	0·56(0·05)	0·45(0·03)

Values are mean(s.e.m.) $^*P < 0.02$ *versus* sham operated and control groups (Mann–Whitney *U* test)

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Role of endotoxin and nitric oxide in the pathogenesis of renal failure in obstructive jaundice

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Background There is an increased incidence of postoperative renal failure in patients with obstructive jaundice. The purpose of this study was to investigate the role of endotoxaemia and nitric oxide in this association.

Methods In bile duct-ligated, sham-operated and control rats, plasma total bilirubin levels, creatinine clearance and plasma endotoxin were determined. Endothelium-dependent vasodilatation to acetylcholine, and endothelium-independent vasodilatation to nitroglycerine and forskolin were evaluated in isolated perfused rat kidney.

Results Twenty-one of 27 bile-duct ligated rats had endotoxaemia. Plasma bilirubin levels were higher and creatinine clearance was significantly reduced in the bile duct-ligated endotoxin-positive group compared with values in the other groups. Furthermore, in the isolated perfused rat kidney from rats with endotoxaemia, basal perfusion pressure and renal vascular relaxation to acetylcholine and nitroglycerine which is mediated by guanosine cyclic 3′, 5′-cyclic monophosphate (cGMP) were significantly reduced, but relaxation to forskolin mediated by adenosine cyclic 3′, 5′-cyclic monophosphate did not change.

Conclusion Endotoxaemia in obstructive jaundice may induce overproduction of nitric oxide that may lead to impairment of cGMP-associated vasodilatation and disrupt autoregulation of the renal vascular bed. This may contribute to renal failure in obstructive jaundice.

Renal impairment is extremely common in the presence of obstructive jaundice, with 60–75 per cent of patients having a fall in postoperative glomerular filtration rate[1,2]. The incidence of acute renal failure and the mortality rate in patients with jaundice are high[3–5].

Although the exact aetiology of renal dysfunction in jaundiced patients remains elusive, a number of factors have been implicated, including increased serum levels of bile salts[6,7], alterations in renal and systemic haemodynamics due to increased renin–angiotensin–aldosterone[8], atrial natriuretic peptide[9,10] or prostaglandins[8,11–13], extracellular fluid depletion[14,15], cardiac dysfunction[16] and inhibition of mitochondrial phosphorylative activity[17]. Since Wardle and Wright first suggested the association between endotoxaemia and obstructive jaundice in 1970[18], there has been increasing evidence that gut-derived endotoxins are the prime cause of renal dysfunction in patients with biliary obstruction[1,19,20].

The effects of endotoxin are most likely to be mediated by the action of various cytokines[21]. Cytokines are capable of impairing renal function through two main effects: alteration of renal haemodynamics and a direct action on the kidney[5]. Recently, Valance and Moncada[22] have focused on nitric oxide as a mediator of the hyperdynamic circulation and renal failure in cirrhosis. Nitric oxide, an important regulator of vascular tone, has been suggested as a mediator of the haemodynamic changes involved in sepsis and cirrhosis[23]. Raised levels of nitric oxide were inversely related to systemic vascular resistance and correlated positively with increased serum endotoxin levels[24].

The aim of this study is to evaluate the relationship between the renal impairment and endotoxaemia, and also the reactivity of the renal vascular bed, in jaundiced rats.

Materials and methods

Surgical procedures

Wistar rats ($n = 83$) weighing 180–280 g of either sex were used. All animals were allowed standard rat chow and water *ad libitum*. Before the surgical procedures, animals were individually housed in metabolic cages, urine was collected for 24 h and then tail vein blood samples were obtained. Assays were performed on plasma and urine samples for baseline determination of plasma bilirubin level and creatinine clearance.

The rats were randomly divided into three groups The first group had bile duct ligation, which was performed under ether anaesthesia. A central upper abdominal incision was made, and the common bile duct was identified, doubly ligated with 4/0 silk ligatures and divided At the end of the procedure, the abdomen was closed and the animal was allowed to recover. The second group underwent sham operation, animals were operated on as above, but the common bile duct was identified and freed from the surrounding tissue without ligation and division. Rats in the control group did not have any surgical procedure.

Three weeks later, the rats were returned to the metabolic cages and 24-h urine collections were performed as described previously. Fourteen rats died within a few days either from the effects of anaesthesia or from biliary peritonitis, and were excluded from further analysis.

Preparation of perfused kidneys Rats were anaesthetized with urethane 1·6 g/kg by intraperitoneal injection. After laparotomy with a midline incision, sodium heparin 500 units/kg was injected into the aorta. The aorta was ligated distal to the right renal artery and a polypropylene cannula was inserted into the renal artery through an aortotomy incision. The ureter and renal vein were transected to eliminate any resistance to urine flow and venous discharge. The left kidney was removed and placed into the perfusion system using a renal artery cannula. In the

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with incisional hernia operated between 1977 and 1995. Since hernia recurrence is strongly related to tissue tension the authors measured prospectively the tension resulting from approximation of fascial borders at the time of the operation in 52 patients since 1992. When tension was below 1·5 kp (kilopond) direct repair was performed and when it was 1·5–3·5 kp direct repair with mesh reinforcement was carried out. If tension exceeded 3·5 kp fascial borders were approximated until tension reached 3·5 kp and then a mesh was inserted to cover the remaining defect. When this is necessary the authors excise the hernial sac and suture it to the mesh to avoid direct contact between small bowel and the mesh. Using this algorithm recurrent incisional hernias were recorded in 2–22 per cent of patients compared with 38–44 per cent of patients in the historical control group without tension mesurement. Again no difference in recurrence rates was observed when direct suture and Mayo reconstruction were compared in the earlier group. The authors suggest that intraoperative tension control allows a staged repair of incisional hernia and results in low recurrence rates.

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bilateral graft replacement giving early mortality rate of 8 per cent. Mean(s.d.) actuarial long-term survival was 78(11) per cent at 5 years. The authors conclude that bilateral transplantation is followed by better pulmonary function and unilateral transplantation, although allowing more patients to receive a graft, should therefore be restricted to patients in whom the expected perfusion/ventilation mismatch after unilateral transplantation is small.

Orthopaedic surgery

Injury to ankle ligaments following torsion trauma used to require operative treatment until approximately 10–15 years ago. Today operative reconstruction of injured ankle ligaments has been replaced by more conservative treatment approaches using tape dressings. In a report from Bochum[15] the treatment for Weber type B fractures of the fibula has been reviewed with a particular interest in conservative treatment of stable fractures with minimal dislocation. Between December 1990 and May 1994 a prospective study was performed in 146 patients with fibular fracture type Weber B. Eighty-five patients were managed conservatively; 23 patients were treated with a below-knee plaster cast for 6 weeks and 62 patients received functional treatment using an ankle brace. Sixty-one patients with a fracture dislocation of more than 2 mm were treated by internal osteosynthetic fixation. Follow-up was complete for 136 of the 146 patients (93 per cent) with a mean follow-up of just under 20 months. Functional treatment following conservative management was possible in 62 of 85 and in 42 of 61 patients treated by internal fixation. Functional results according to Olerud Score were better for patients receiving functional treatment, independent of whether initial treatment had been conservative or operative. The authors conclude that conservative management is feasible in patients with stable fractures and that results are best when early functional treatment can be exercised.

Inguinal hernia

A large number of techniques have been proffered in recent years for treatment of inguinal hernia. Again some groups have critically reviewed their experience with different techniques of hernia repair for primary and recurrent inguinal hernias. A prospective study[16] of transabdominal preperitoneal (TAPP) mesh repair was carried out in preparation for a planned randomized trial in 94 patients from June 1992 to February 1994 and 100 patients were treated from March 1993 to November 1994 by Lichtenstein patch closure. All TAPP operations were performed by one experienced senior surgeon whereas 11 other surgeons in the same department, many of them in training, performed the Lichtenstein repair. Operative times were 65 min for the TAPP repair and 55 min for open patch closure. There were two intraoperative complications for the laparoscopic method: bleeding and subcutaneous emphysema. Analgesic requirements were higher for the open procedure, but on a visual analogue scale differences were less pronounced. Thirteen postoperative complications were recorded for the laparoscopic method *versus* 18 for the open patch repair. Mean follow-up was 30 months for laparoscopically-treated patients compared with 22 months for patients treated by Lichtenstein repair. Hospital stay was similar (7 *versus* 8 days), but patients who had laparoscopy returned earlier to work (14 *versus* 19 days). Most importantly, however, the laparoscopic group developed eight recurrent hernias compared with no recurrence in the Lichtenstein group. The authors summarized that open patch repair is easy to learn and has a low recurrence rate; it can be performed under local anaesthesia and its cost is comparatively low (£300). Since open repair appeared to be superior the planned randomized trial was not performed and laparoscopic hernia repair is no longer performed in this department.

In a study from Stuttgart[17] laparoscopic repair using the TAPP method was evaluated for the treatment of recurrent inguinal hernia following open anterior primary operation. Between April 1993 and December 1995 a total of 210 recurrent hernias were entered into the study representing 16 per cent of all hernia operations in this department. Median operative time was reduced from 60 min in the first 50 patients to 55 min for more recent patients. The total complication rate was 4 per cent and this also appeared to be less for more recent operations, confirming some degree of learning in the authors' opinion. Routine sonography identified asymptomatic wound seroma in 22 per cent of patients, which resolved spontaneously after 4–6 weeks. Median follow-up was 16 months. Two recurrences were observed and more than 80 per cent of patients followed up for more than 1 year were asymptomatic. The authors also recorded the time for return to work in 74 patients to whom this was applicable. Median time off work for all patients was 21 days: 10 days for self-employed patients, 21 days for white collar employees and 37 days for blue collar.

Incisional hernia

Incisional hernia may be expected in up to 10 per cent of patients undergoing abdominal operations. Recurrence rates following incisional hernia repair of up to 50 per cent have been reported. In a retrospective study from Aachen[18] the authors review their experience with preperitoneal mesh repair of incisional hernia. In the 8-year period 1987–1994, 245 patients presented with 272 incisional hernias. Of these, 161 patients presented with recurrent incisional hernia. Primary hernia repair without mesh was performed in 190 patients, while 82 patients had mesh reinforcement of the abdominal wall (61 patients had preperitoneal mesh repair). Comparison of repair with and without mesh showed that mesh repair was followed by more complications (51 *versus* 23 per cent). However, recurrence rates were lower when a mesh was used; this was true for small hernias (less than 4 cm diameter: mesh 0 per cent *versus* no mesh 43 per cent) and large hernias (more than 4 cm diameter: mesh 12 per cent *versus* no mesh 34 per cent). No major differences in terms of recurrence rates were observed when absorbable and non-absorbable suture materials were compared, and when Mayo reconstruction was compared with direct suture techniques. Although preperitoneal mesh repair had the lowest recurrence rate, currently available mesh material often caused late complaints of stiffness and paraesthesia, and 25 per cent of patients complained of impaired mobility. The authors conclude that mesh repair for incisional hernia should be used carefully and that mesh material should be improved.

The problem of incisional hernia was also addressed in a diligent study from Erlangen[19] including 678 patients

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Digest

Der Chirurg

For this quarter's digest, Professor Christian Herfarth and Dr Thomas Lehnert have selected the best from the October to December 1996 issues of *Der Chirurg*. A digest for the *BJS* for the same period, written by Mr Colin Johnson, appears in the German journal.

Reviews

Reviews of the year's last quarter include series of articles focusing on head injury[1–4], fractures of the lower extremities[5–8], molecular diagnosis[9], gene therapy[10] and telemedicine[11]. Finally, in a series of articles including contributions from Belgium, Austria and Germany, surgical therapy for chronic pulmonary emphysema is reviewed.

Lung volume reduction surgery

Pulmonary emphysema has become one of the leading causes of death from chronic lung disease. No effective medical treatment is available, since most of the morphological changes associated with long-standing disease are irreversible. A number of surgical approaches to improve pulmonary function have been devised, but only in the 1950s was it shown by Brantigan and Mueller that reduction of diseased pulmonary parenchyma results in improved oxygenation and pulmonary function. At the time this procedure did not gain popularity, because of the high postoperative mortality rate associated with pulmonary parenchymal fistula and subsequent empyema. Today the techniques of parenchymal resection have been improved and lung volume reduction surgery has experienced a rejuvenation. Stamatis and colleagues[12] from Essen review now the principles and current practice of lung volume reduction and report their experience with this operation.

Patients were candidates for lung volume reduction, when (1) chest radiography, computed tomography and perfusion scintigraphy demonstrated target areas for volume reduction preferably at basal or apical lung portions allowing a 20–30 per cent reduction of affected lung parenchyma; (2) severe obstruction was present after administration of broncholytic agents with reduction of the forced expiratory volume in 1 s (FEV_1) to 1·0–1·2 litres or below, or to less than 20–35 per cent of predicted values; or (3) total lung volume measured more than 120 per cent or residual volume more than 200 per cent of predicted volume. Exclusion criteria were age above 75 years, concurrent infection, arterial partial pressure of oxygen less than 50 mmHg (at increased arterial partial pressure of carbon dioxide (Pa_{CO_2})), Pa_{CO_2} 50 mmHg or more, pulmonary hypertension (mean pulmonary artery pressure 35 mmHg or greater, requiring more than 20 mg prednisolone (or equivalent) per day), smoking or alcohol abuse, body mass index 75 per cent or less, lack of rehabilitation facilities, generalized pulmonary or pleural disease, severe medical illness or severe osteoporosis.

Preoperative rehabilitation of the severely compromised pulmonary function and overall physical condition of the patients was mandatory. If secretions obtained at bronchoscopy harboured bacteria or if *Pseudomonas* was demonstrable in sputum, antibiotics were administered prophylactically. All patients demonstrating severe emphysema were considered potential candidates for bilateral volume reduction. Unilateral lung volume reduction should be reserved for patients with predominantly unilateral emphysema, lateralization of target areas on perfusion scintigraphy, pleural adhesions, previous operations to the respective lung or severe general illness with increased perioperative risk.

Between June 1994 and June 1996 a total of 58 patients underwent unilateral or bilateral lung volume reduction. The mean(s.d.) age of the 14 women and 44 men was 59(9) (range 35–72) years. Open surgery was performed in 50 patients and eight patients were treated by video-assisted thoracoscopy. Stapler instruments were used throughout and staple lines were reinforced with bovine pericardial strips in the most recent 47 patients. There were no major intraoperative complications and all but two patients were extubated in the operating room. Two patients died to give a 90-day mortality rate of 3 per cent. Complications reported were pneumonia ($n = 7$), air leak of more than 7 days' duration ($n = 14$), subcutaneous emphysema ($n = 4$) and delayed wound healing ($n = 2$). One patient in whom adhesiolysis was performed required reoperation for persistent bleeding. There was a significant improvement for both unilateral and bilateral volume reduction compared with preoperative values. Postoperative test results for patients with unilateral volume reduction were in the same range as those of patients with bilateral volume reduction. Although lung volume reduction has been beneficial to most of their patients, the authors emphasize that despite the sometimes euphoric reports of lung volume reduction surgery this treatment is given to severely ill patients requiring most intensive perioperative and postoperative care. Long-term results of the operation are as yet unknown and therefore the procedure must still be considered experimental.

In a similar protocol from Vienna[13] operations were performed by video-assisted thoracoscopy in 27 of 54 patients. The overall mortality rate was 9 per cent. This group reported no significant differences when open volume reduction was compared with thoracoscopic operations, but patients with bilateral volume reduction had better postoperative pulmonary function tests than those undergoing unilateral operation. The authors speculate that video-assisted thoracoscopy is superior to open thoracotomy and volume reduction.

If medically intractable disease is too far advanced to allow volume reduction then patients may be candidates for lung transplantation. Patients must be carefully selected, however. They should not be older than 55 years and expected life span should be less than 24 months with conservative treatment[14]. Between 1989 and 1995 a total of 25 patients received lung transplants for chronic obstructive pulmonary disease. Six patients received unilateral grafts and 19 patients received whole grafts. Mean preoperative vital capacity was 2·2 litres, mean FEV_1 was 0·76 litres and mean(s.d.) pulmonary artery pressure was 29(9) mmHg. Mean postoperative vital capacity was 2·7 litres for unilateral and 4·4 litres for bilateral grafts. FEV_1 was 1·4 and 3·0 litres respectively. One patient died in each group with unilateral and

Recurrent 'abscesses' occurring in the thyroid area in children are due to branchial anomalies. Their origin is located close to the oesophageal inlet at the pyriform sinus. The key for the diagnosis comes from laryngo-hypopharyngoscopy. These anomalies sometimes result in tracts or cysts in the deeper parts of the neck, down to the supraclavicular or thoracic areas. Three cases were reported by Contencin *et al.*[17], from Paris. After recovery from the infectious process, these anomalies have to be treated by mucosal suture of the pyriform sinus. The recurrent laryngeal nerve was identified and a small piece of cartilage was removed in all cases. The authors concluded that, if these diagnostic and therapeutic procedures are used at the first infectious episode, they may prevent the occurrence of repeated thyroid abscesses in children.

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of French Cancer Registries (FRANCIM) provides accurate and reliable knowledge on medical practices, geographical variations, trends and quality control, and that such information is required to plan healthcare policy.

Mansvelt and co-workers[11], from Haine Saint Paul in Belgium, treated 28 patients with peritoneal carcinomatosis arising from intra-abdominal cancer by intraperitoneal hyperthermic perfusion. Mitomycin C, diluted in 3 litres of saline solution warmed to a mean temperature of 45°C, was injected into the abdominal cavity for 1 h. Median survival for the whole series (postoperative mortality included) was 260 days, and for 19 patients with complete resection of carcinomatous nodules larger than 3 mm it was 450 days. Only five of the 28 patients developed ascitic effusion during follow-up. For the authors, these results confirm the efficacy of intraperitoneal hyperthermic perfusion on ascitic effusion and on the survival rate in patients with nearly complete resection of peritoneal carcinomatosis.

Laparoscopic surgery

Some 150 patients treated by laparoscopic cholecystectomy were included in a prospective study to compare intraoperative cholangiography and laparoscopic ultrasonography[12]. The biliary tree was successively examined by the two methods in the systematic detection of common bile duct stones. The feasibility of laparoscopic ultrasonography was 100 per cent. Cholangiography was performed in only 125 cases (83 per cent). The duration of laparoscopic ultrasonography was significantly shorter (11·6 *versus* 17·6 min, $P = 0{\cdot}0001$). Common bile duct stones were found in 14 patients (9 per cent). For laparoscopic ultrasonography, sensitivity was 80 per cent and specificity was 99 per cent, compared with 78 and 97 per cent respectively for cholangiography. The combination of the two examinations had 100 per cent sensitivity and specificity. Laparoscopic ultrasonography failed to recognize the intrapancreatic part of the bile duct (25 patients (17 per cent)), and did not show anatomical anomalies detected by cholangiography.

A study to evalute the results of laparoscopic treatment of appendicitis with peritonitis was conducted by Fabiani *et al.*[13], from Nice. Some 32 patients (16 men; mean age 43 years) underwent emergency laparoscopy with a clinical diagnosis of localized or generalized peritonitis. All patients had double antibiotic therapy for at least 7 days. The laparoscopic appendicectomy technique included insufflation to 12 mmHg, introduction of three cannulas, peritoneal lavage, coagulation of the mesoappendix, ligature of the base of the appendix and no drainage. There were four conversions. Nine of the 28 patients treated completely by laparoscopy presented with generalized peritonitis and 19 had localized peritonitis (including eight abscesses). The mean operating time was 86 min. There were no deaths. Three of the 28 patients had postoperative morbidity. The mean duration of postoperative ileus was 2·8 days. Mean hospital stay was 6·8 days. There was no bowel obstruction or incisional hernia at a mean follow-up of 28·5 months. The authors concluded that the laparoscopic treatment of appendicular peritonitis is possible, simple, reproducible and effective, without any specific complications. The advantages of laparoscopic techniques over the traditional large incisions are the absence of parietal complications, the quality of exploration and peritoneal lavage, and improvement of postoperative comfort.

Urology

In France, two to three million women suffer from urinary incontinence. The cure rate for the abdominal retropubic colposuspension (Burch procedure) is 85 per cent after 5 years. Since 1991, laparoscopic retropubic colposuspension has been advocated for the treatment of urinary stress incontinence. Grossmann *et al.*[14] from Paris reported on 578 patients, with a conversion rate of 4 per cent. The most frequent complication of colposuspension is bladder injury. The majority of cystotomies were treated laparoscopically. Follow-up in this series is relatively short. After 1 year, the success rate was 96 per cent. However, these results require confirmation by other series with longer follow-up and by prospective randomized studies.

Pelvic recurrence of cervical cancer is a life-threatening event for patients. The main therapeutic challenge is to achieve local control. Martino *et al.*[15], from Marseille, presented their experience of the surgical treatment of pelvic cervical cancer relapses in 49 patients. Forty-four tumour relapses were localized in the pelvis and five were associated with distant metastasis. Surgery alone was performed in 31 cases and in association with radiotherapy in 18. There was a significant correlation between the initial stage, the site of tumour relapse and surgical curability. The overall actuarial survival rate was 44 and 24 per cent at 2 and 5 years respectively. After curative treatment, the actuarial survival rate was 71 and 47 per cent at 2 and 5 years respectively. There was a major surgical complication in 14 patients; 11 reoperations were performed. Surgical treatment is a worthwhile palliation in selected patients with pelvic sidewall infiltration, because it is often the only available therapeutic option.

Thyroid

Goudet and colleagues[16] from Dijon, using a matched study technique, evaluated the operative morbidity rates in patients operated on for substernal goitre. Each substernal goitre was compared with a cervical goitre for surgical technique, histology and thyroid function. There were 97 patients with substernal goitres (75 per cent in women), 43 per cent with normal thyroid function, 28 per cent with mild hyperthyroidism and 29 per cent with hyperthyroidism. Mean(s.d.) age was 66·5(11·5) years *versus* 55·8(11·9) years for cervical goitre ($P < 0{\cdot}001$). The proportion of men was higher for substernal than for cervical goitre (25 *versus* 10 per cent, $P < 0{\cdot}01$). Early hypoparathyroidism occurred in 3 and 2 per cent ($P = 0{\cdot}5$), and late hypoparathyroidism in 1 *versus* 0 per cent ($P = 0{\cdot}5$). There was a drop of 10 mg/l in serum calcium concentration in both groups but no change in serum phosphate levels was noted. The early recurrent laryngeal nerve palsy rate was 4 *versus* 0 per cent ($P = 0{\cdot}06$) and 3 *versus* 0 per cent 1 year later ($P = 0{\cdot}12$). The early postoperative reoperation rate for haemostasis was 2 and 1 per cent ($P = 0{\cdot}25$). The authors concluded that there is no significant difference in surgical morbidity between thyroidectomy for substernal and cervical goitres when patients are operated on in specialized centres.

concluded that the 2-year recurrence rate of intraperitoneal expanded PTFE hernia repair is not very different, after the learning phase, from that of many other procedures. However, the expense of these patches means that this technique should be used only when other efficient procedures are not feasible, for example in the challenging treatment of recurrent hernia after failure of preperitoneal prosthetic hernioplasty.

Johanet *et al.*[6], from Paris, reported the immediate results of patients with inguinal hernia operated on as day cases. Some 367 consecutive patients (433 cures) were operated on during the study period; 197 (207 repairs) had ambulatory surgery (54 per cent), of whom 176 (89·3 per cent) returned home at night. The reasons for an inpatient procedure were bilateral repair in 43 cases (25·2 per cent), medical in 28 (16·4 per cent), surgical in 34 (20·0 per cent), social in 23 (13·5 per cent), other in 29 (17·0 per cent) and 13 miscellaneous. The unilateral nature of the repair and young age were two factors that led to the use of ambulatory surgery.

Pancreas

A study was conducted by Kestens *et al.*[7], from Brussels, to assess the long-term results of a new surgical technique for the treatment of patients suffering from painful chronic pancreatitis. From 1981 to 1994, 54 patients with chronic painful pancreatitis underwent an original duct drainage procedure, named by the authors 'double drainage' because it consists of a large transduodenal sphincterotomy and a long pancreatic duct opening, accompanied by recanalization of the cephalic pancreatic duct. This procedure was used exclusively for type I pancreatitis with major lesions in the head of the gland (calcified stones, narrowing of the ducts, inflammatory process). There were 40 men and 14 women in the series. No perioperative death occurred and a low morbidity rate (22 per cent) was observed. Mean follow-up in 52 patients was 56 (median 59·5) months. The 5-year actuarial survival rate was 85 per cent, and 81 per cent were free of pain (91 per cent when the pancreatic duct was dilated to more than 6 mm, *versus* 63 per cent when it was less than 6 mm, $P<0{\cdot}01$). These excellent results should serve as a baseline for any alternative treatment for this category of patients with painful chronic pancreatitis.

In a prospective study carried out by Champault *et al.*[8] from Bondy, France, 26 patients with pancreatic and periampullary cancer were evaluated with ultrasonography, computed tomography (CT), endoscopic ultrasonography and laparoscopic ultrasonography. Criteria for non-curative resection were visceral extension, portal pedicle extension, portal or mesenteric invasion, and hepatic or peritoneal deposits. Five of the 26 patients had a curative Whipple procedure. The sensitivity of percutaneous ultrasonography and CT were comparable, although CT appeared to evaluate better the size of the tumour and lymph node involvement. Some 50 per cent of patients had at least one criterion for non-curative resection. Endoscopic ultrasonography had good sensitivity for the staging of small tumours (less than 20 mm) (six patients), detection of adjacent nodes (five) and the relation between tumour and mesenteric or portal veins (two). Endoscopic ultrasonography was not able to detect peritoneal and/or liver micrometastases (44 per cent of which are missed by this examination alone). With this examination, a contraindication to curative resection was found in 58 per cent of patients. Laparoscopic ultrasonography assessed accurately all tumours larger than 3 cm, but, compared with endoscopic ultrasonography, the accuracy was not as good for small tumours and adjacent nodes; it was equal for the venous relations with tumours, but was better for microperitoneal (ten *versus* one) or hepatic (15 *versus* four) metastases. The prediction of non-curative resection was 81 per cent (21 of 26). For the authors, these results suggested that percutaneous ultrasonography and CT should be used as first-line procedures in preoperative staging and assessment of resectability of pancreatic cancer. When the patient does not appear to have disseminated lesions (50 per cent), endoscopic ultrasonography gives a good estimation of the size of the tumour, node assessment and vascular relations. Laparoscopic ultrasonography should be the first step in a curative surgical treatment. Laparoscopic ultrasonography revealed 15–30 per cent of unknown micrometastases and avoided useless laparotomy in these patients.

Two patients with mucinous duct ectasia were reported by Quandalle *et al.*[9] from Lille, France. Epithelial changes were spread along the pancreatic duct and ductal ectasia was diffuse. Multifocal infiltrating carcinoma was observed in one patient; microinvasive carcinoma located in the head of the pancreas was observed in the other. Morphological features assessed by CT, endoscopic ultrasonography and pancreatography were useful for preoperative diagnosis of mucinous pancreatic duct ectasia. In one case, malignancy was suggested by measurement of tumour markers in cyst fluid aspirated during percutaneous pancreatography. Total duodenopancreatectomy was performed in both cases. The two patients were alive and disease-free with a follow-up of 18 and 36 months.

Colon and rectum

Improvement of healthcare policy requires an assesssment of healthcare practices. In France, morbidity registries might be the best tool for such an assessment. Three studies conducted by Maurel *et al.*[10], from Caen, France, show how the treatment of rectal cancer can be assessed by French Cancer Registries. The first was a cross-sectional study on data from seven French departments in 1990, representing a population of 3 841 678 residents and 427 rectal cancers; the second was a longitudinal study on data from two Digestive Cancer Registries, between 1978 and 1990, representing 1131 tumours; the third was a regional audit concerning quality control in 505 rectal resections for cancer in Normandy between 1988 and 1993. In 1990, the mean resection rate was 77·8 per cent. The sphincter preservation rate also increased significantly to 53·9 per cent in 1990. The use of adjuvant radiotherapy increased significantly between 1978 and 1990, more rapidly in university hospitals. In more recent years, radiotherapy was used in 50 per cent of patients with resected rectal cancer, with no differences between the various types of healthcare centre. However, in 1990, major geographical variations were observed for the use of adjuvant radiotherapy. The use of reproducible quality criteria for resection (length of distal excision, number of nodes examined and histological status of lateral margins) showed a global deficiency and marked variations between the various types of healthcare centres and levels of surgical training. The authors concluded that the network

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Annales de Chirurgie

Digest

For this quarter's digest, Dr Denis Castaing, Editor of *Annales de Chirurgie*, chooses the best from issues nine and ten of 1996 and issue one of 1997. A reciprocal digest written by our European Editor, Mr Colin Johnson, appears in the French journal.

Inguinal hernia

Repair of inguinal hernia still constitutes an unresolved problem, which has been brought up to date by the introduction of laparoscopic surgery as a treatment option. Issue nine of *Annales de Chirurgie* was dedicated to this old surgical problem.

Izard *et al.*[1], from Tarbes, France, reported on 1332 patients with a hernia operated on by the same surgeon between 1979 and 1992. From 1979 to 1984 McVay's technique was used; after 1985 dissection and preservation of all the nervous ramifications of the groin was added to this. The recurrence rate was less than 3 per cent. Systematic complete nerve preservation decreased residual pain and all forms of functional symptoms by a factor of three. The number of patients with minor symptoms, often minimal and transient, decreased from 24 to 8 per cent, but, most importantly, the proportion with major symptoms, discomfort on effort, and persistent and disabling pain decreased from 3 to 1 per cent. The authors concluded that McVay's technique is perfectly suitable for indirect and direct inguinal hernias, which represent 90 per cent of all hernias. Very large hernias with abdominal wall deterioration or recurrent hernias, especially when the initial surgical repair appeared to be satisfactory, would be better treated by direct or retroperitoneal insertion of a prosthesis.

To analyse the possibility of nerve injury during hernia repair, Chevallier *et al.*[2] from Paris studied the anatomical relations of these nerves with the subperitoneal fascia transversalis and inguinal fossae. This anatomical study, consisting of dissection of non-embalmed cadavers after evisceration, allowed dissection of the lumbar plexus and its terminal branches, particularly those supplying the inguinofemoral region: iliohypogastric and ilioinguinal nerves, the genitofemoral nerve, the femoral nerve and the lateral cutaneous nerve of the thigh. When seen by transperitoneal laparoscopy, the posterior surface of the anterior abdominal wall is centred on the deep inguinal ring, containing testicular vessels and the vas deferens. This deep inguinal ring receives the genitofemoral nerve. Medially, the anterior parietal peritoneum has three folds formed by the outline of the epigastric artery, umbilical artery and urachus on the midline. The outline of Hesselbach's ligament separates the deep inguinal ring from Hesselbach's triangle, the zone of weakness of direct inguinal hernia. Installation of an abdominal wall prosthesis, either transperitoneally or retroperitoneally, must be centred on the deep inguinal ring, and its solid sutures should be located medially to the pectineal ligament and anterior abdominal wall. The nerves at risk of being damaged are situated laterally. No stapling must be performed under the plane of the inguinal ligament to avoid damage to the femoral vessels, or lateral to the deep inguinal ring to avoid nerve damage.

Between October 1992 and September 1994, Hauters *et al.*[3] from Tournai, Belgium, randomly assigned 70 patients with unilateral hernia either to transabdominal preperitoneal laparoscopic repair (35 patients) with a 3 × 5-inch polypropylene mesh or to conventional Shouldice repair (35). The series consisted of 60 men and ten women, with a median age of 56 years. According to the Nyhus classification, there were 25 type 2, 24 type 3a and 21 type 3b hernias. These preoperative characteristics were equivalent in both groups. Comparing the laparoscopic with the Shouldice group, the mean(s.d.) operating time (65(20) min) and postoperative hospital stay (3·8(1·3) days) were similar. Postoperative pain was evaluated on a visual analogue scale (scored from 0 to 10) on the first and third postoperative day. Mean(s.d.) scores were 3·4(1·5) and 1·3(1·4) respectively in the laparoscopic group and 5·3(1·9) ($P < 0.001$) and 2·8(1·8) ($P < 0.005$) in the Shouldice group. Significant morbidity occurred in seven patients having laparoscopic repair (three seromas and four cases of orchitis) and in five in the Shouldice group (one wound abscess, two cases of chronic neuralgia and two cases of orchitis). A quicker return to home activities in the laparoscopic group (6(2) *versus* 10(4) days in the Shouldice group, $P < 0.05$) was recorded but time off work was similar in both groups (30(9) days). All patients were evaluated, with a median follow-up of 30 (range 19–42) months. There was one recurrence in the laparoscopic and three in the Shouldice group. Statistical analysis revealed that the recurrence rate, for patients older than 50 years and presenting with a type 3 hernia, was higher in the Shouldice group (three of 14) than in the laparoscopic group (none of 13).

In conclusion, compared with Shouldice repair, laparoscopic herniorrhaphy is associated with less postoperative pain, a quicker return to everyday activities and similar postoperative morbidity. A similar conclusion was reached by Johanet *et al.*[4], from Paris, following a series of 790 laparoscopic repairs with a transabdominal preperitoneal approach. The complication rate in patients requiring surgical revision was 11 of 790 (1·4 per cent): four haematomas, two seromas, two wound dehiscences, one case of peritonitis, one of local sepsis and one urethral stenosis. None of these complications was related to the transpreperitoneal approach and all but one of them occurred during the first 2 years of the authors' experience. The recurrence rate for patients with follow-up of more than 2 years was 5 per cent. With experience, the size of the mesh has gradually increased.

Gillion *et al.*[5], from Thiais, France, reported the results of a prospective multicentre study (group Cure des Hernies Inguinals sous Coeliosofie) of 184 cases (in 155 patients) of laparoscopic herniorrhaphy using an intraperitoneal expanded polytetrafluoroethylene (PTFE) patch and followed for at least 2 years. Twelve recurrences (6·5 per cent) were found in 11 patients; ten of the 12 occurred within the first year after operation. After each surgeon's 20th laparoscopic herniorrhaphy, the recurrence rate was three of 113 (2·7 per cent) ($P < 0.05$). Late local pain around the patch and its staples was found in 12 patients (slight in ten cases, mild in one and serious in one). Local hypoaesthesia of the upper internal part of the thigh was found in one patient. No testicular atrophy or intraperitoneal complication was observed. The authors

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response is beneficial for the patient in the longer term. Further clinical and basic scientific research will be required to develop the global picture of SIRS, its associated family of syndromes and their natural histories. Modulation of SIRS/CARS remains in its infancy.

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administration after the onset of sepsis carries no benefit[30,137–140]. Pentoxifylline and amrinone are phosphodiesterase inhibitors that lead to increased intracellular levels of adenosine 3′,5′-cyclic monophosphate which interrupts intracellular signalling[141,142]. Pentoxifylline decreases TNF-α synthesis in a murine model of endotoxic shock, while amrinone has been shown to be a more potent inhibitor of LPS-stimulated TNF-α synthesis[143–145]. In humans, pentoxifylline is able to decrease TNF-α but not IL-6 and IL-8 serum concentrations, and to decrease augmented PMN reactivity during septic shock[146,147]. Biologically-derived glucan infusions improve immune function after trauma and after high-risk abdominal surgery[148,149]. Taurolidine is considered to be a non-specific LPS antagonist. It has no beneficial therapeutic effect on the outcome of patients admitted to the intensive care unit with sepsis syndrome, using progression, resolution of organ failure and 28-day mortality rate as markers of outcome[150].

Arachidonic acid metabolites help mediate haemodynamic alterations in SIRS/sepsis[36,151–153]. Indomethacin given 1 h before or after a bolus of TNF-α blocks metabolic acidosis, shock and death in rats[154]. Similarly, ibuprofen has also been shown to be effective in animal models[155,156]. However, it has no effect in man[157]. Leukotriene inhibitors have been shown to be beneficial in septic shock[158]. Combined therapies to inhibit several components of the arachidonic acid pathways are more effective than single drug therapy in protecting animals from progressing to MODS[159,160].

Specific PAF receptor antagonists provide protection against the fatal complications of endotoxic shock in animal models[106,107]. In patients, the use of PAF antagonists has shown no benefit[161]. Activation of the kallikrein–kinin system in sepsis has long been recognized and, experimentally, bradykinin antagonists have been shown to be beneficial in Gram-negative sepsis[162].

Newer concepts in systemic inflammatory response syndrome

With failure of the single agent therapies to control SIRS, several authors have suggested that there is a fundamental misconception of the disease process within the human body. SIRS, which is proinflammatory, is only one side of a two-sided response. The other side is an anti-inflammatory response termed the compensatory anti-inflammatory response syndrome (CARS)[163]. The rationale for this theory is that many of the proinflammatory mediators, particularly the interleukins, that participate in SIRS can inhibit immune function by decreasing monocyte/macrophage, B cell and T cell function. In addition, the proinflammatory mediators can inhibit their own synthesis or enhance the synthesis of natural antagonists. Cumulatively, these responses are the body's attempt to re-establish homeostasis, and result in anergy and increased susceptibility to infection. Thus, at any one time there is a battle between the 'Ying' and 'Yang' of the inflammatory system which clinically manifests itself as SIRS, CARS or an intermediate, mixed inflammatory response syndrome (MARS). The spectrum of consequences of these responses has been termed CHAOS (Cardiovascular shock, Homeostasis, Apoptosis, Organ dysfunction and immune Suppression)[163,164]. This new set of concepts suggests that if SIRS is predominant, conventional antimediator or antagonist therapies will be of value, but if CARS is predominant, then novel immune stimulants or antiantagonist therapies will be required. To enter this algorithm, a fundamental step will be required, that of achieving a diagnosis of the systemic inflammatory state of the patient (SIRS, CARS or MARS).

Conclusion

The consensus definition of SIRS has allowed translation of several unrelated disease states into a universal process from which it will be possible to categorize, research and treat the body's normal and abnormal inflammatory response to any insult. For surgeons, it forms the basis of the physiology and pathophysiology which their patients experience and which they treat in their practice. In the past decade the cellular and humoral events of inflammation and the systemic inflammatory response that can result have been better defined, yet our overall knowledge in this field is still limited. The newer concepts of MARS, CARS and CHAOS in the natural history of SIRS testify to these limitations and suggest possible new horizons to our understanding (*Fig. 5*). At present, attempts to intervene in the cascades that participate in SIRS have met with little success. These unifocal attempts are based on our present knowledge and require pre-emptive therapy which cannot at present satisfy the clinical requirement of controlling SIRS after the cascades have been initiated. It is akin 'to closing the barn door after the horse has bolted'[165]. Furthermore, there is no evidence to refute a contention that part of the SIRS

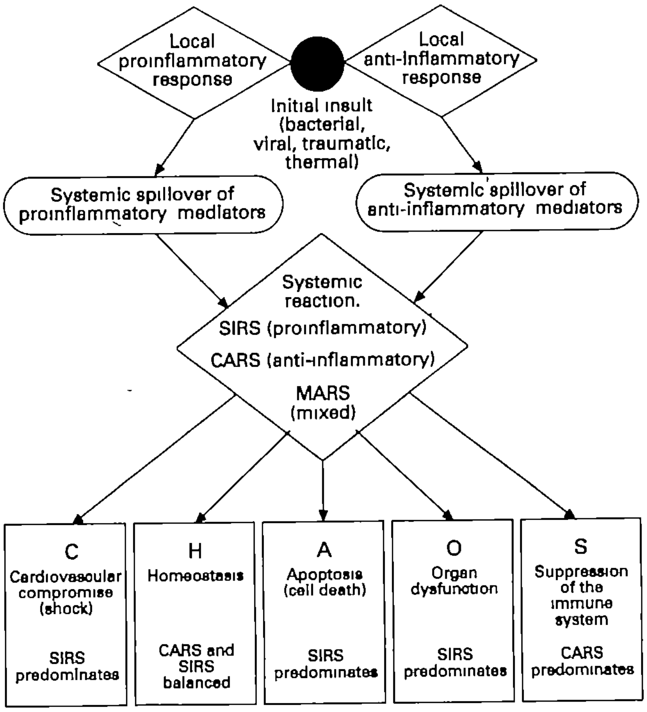
Local proinflammatory response
Local anti-inflammatory response
Initial insult (bacterial, viral, traumatic, thermal)
Systemic spillover of proinflammatory mediators
Systemic spillover of anti-inflammatory mediators
Systemic reaction.
SIRS (proinflammatory)
CARS (anti-inflammatory)
MARS (mixed)
C
Cardiovascular compromise (shock)
SIRS predominates
H
Homeostasis
CARS and SIRS balanced
A
Apoptosis (cell death)
SIRS predominates
O
Organ dysfunction
SIRS predominates
S
Suppression of the immune system
CARS predominates

Fig. 5 The inter-relationship of systemic inflammatory response syndrome (SIRS), compensatory anti-inflammatory response syndrome (CARS) and mixed antagonist response syndrome (MARS) and the CHAOS (Cardiovascular shock, Homeostasis, Apoptosis, Organ dysfunction and immune Suppression) theory. Clinical sequelae of the SIRS and the CARS. (Reproduced from reference 163 with permission from the Society of Critical Care and Williams and Wilkins, Baltimore, Maryland, USA)

hyperalimentation on the immune system[112]. The components of immunonutrition are glutamine, arginine, omega-3 fatty acids and RNA nucleotides. Glutamine has a significant trophic effect on the gut. It is the preferred fuel source for the intestinal tract in times of stress and is a key component in preventing enterocyte loss, atrophy of the mucosa and loss of barrier function. It is also a known fuel for lymphocytes. Arginine has significant immunostimulant effects, with prevention of thymic atrophy, increased production of natural killer and helper T cells, and increased IL-2 release, which stimulates T cell activation. Long-chain omega-6 fatty acids, which are a common component of TPN and TEN solutions, are more significantly immunosuppressive than omega-3 fatty acids. The presence of omega-3 fatty acids leads to a change in the profile of prostaglandins and leukotrienes produced during stress and sepsis (omega-6 fatty acids increase PGE_2 and LTB_4 synthesis while omega-3 fatty acids increase PGE_3 and LTB_5 synthesis). The absence of RNA nucleotides has been shown to decrease the maturation and phenotypic expression of T lymphocytes, to decrease IL-2 production, to inhibit resistance to infection and to diminish T cell-based immunity. There are mixed opinions that nutritional formulae which contain immunomodulators may convey a small benefit over standard formulae. There are some data to suggest that they may be detrimental in certain subsets of patients[112].

Potential therapies

There are three points in the sequence of the pathogenesis of SIRS/sepsis at which therapy can be instituted. First, the nidus of infection can be eradicated with appropriate antimicrobial therapy, surgical drainage, or both. Second, the sepsis-associated cardiovascular metabolic and multiorgan system disturbances can be treated and, third, inhibitors of toxic mediators can be administered[113].

Anti-lipopolysaccharide

LPS comprises complex molecules composed of a polysaccharide side chain (O antigen), attached to a glucosamine-based phospholipid (lipid A) by a 'core' polysaccharide. Polyclonal antisera and monoclonal antibodies to lipid A and core regions of mutant *E. coli* have been developed and tested in clinical trials, some of which have had positive results[114] while others have been negative[115,116]. Two prophylactic studies comparing antiserum with preimmune serum in high-risk surgical patients and in neutropenic patients with cancer did not show a reduction in Gram-negative infections by the administration of antiserum[117,118]. The use of the non-toxic derivatives of lipid A, the presumed toxic moiety of the endotoxin molecule, to attenuate the response to LPS, enhances non-specific resistance to infection and induces tolerance to endotoxin[119–122].

Recently murine and human monoclonal IgM antibodies have been developed using the *E. coli* J5 mutant and have been tested for the treatment of patients with Gram-negative infections in prospective randomized double-blind multicentre trials. In an initial study with E5 murine IgM monoclonal antibody, patients with suspected Gram-negative sepsis were assigned randomly to receive either E5 antibody or placebo[123]. There was no decrease in mortality rates in patients from either group but after subgroup analysis it did appear there was a decrease in mortality rate in patients without shock at the time of entry into the study. A second study concentrating on patients with Gram-negative sepsis but no shock failed to show any benefit with E5[124]. Treatment with a second antibody, HA-1A (human), did not improve overall population survival at 28 days[125]. A subgroup of patients with Gram-negative bacteraemia showed a significantly improved survival at 28 days and this reduction in mortality rate was more pronounced in patients with shock than in those presenting without shock. Unfortunately there were more patients in the placebo arm than in the HA-1A arm who had considerably more risk factors and they received inadequate antibiotic therapy compared with the experimental patients[126]. Other therapies for blocking the LPS-induced phase are soluble CD14 receptors, anti-LPS-binding protein, anti-CD14 receptor antibodies and bacterial permeability increasing protein.

Anti-tumour necrosis factor α

As TNF-α is a primary mediator of the SIRS response, neutralization is an attractive possibility. Antibodies to TNF-α have decreased the mortality rate in models of lethal bacteraemia and, although there was a decrease in 3-day mortality rate in humans, there was no decrease in the rate between patients treated with placebo and a monoclonal antibody against TNF-α at 28 days[127–129]. There are naturally occurring proteins which represent the extracellular domains of the two TNF-α receptors. They act as natural TNF antagonists and prevent septic shock in *E. coli*-treated baboons and death in mice. A chimaeric molecule in which the soluble TNF-α receptor is linked covalently to the Fc portion of IgG has been designed and produced. With a single administration, the chimaeric molecule can significantly improve septic shock in animal models[130]. In patients with septic shock the chimaeric molecule (TNFR:Fc) did not reduce the mortality rate[131].

Anti-interleukin 1

There is a lag time between activation of TNF-α and IL-1 expression. This window of opportunity suggests that targeting IL-1 may be temporally more efficacious than targeting TNF-α. IL-1 receptor antagonists reduced mortality rates in a rabbit model of septic shock even when given after the onset of shock[132]. IL-1RA is a naturally occurring protein which binds to the human IL-1 receptor but has no agonist activity[133,134]. It must be administered in very large molar amounts in order to block IL-1 activity. There is no significant increase in overall survival time in patients treated with IL-1RA[135]. However, there is a significant increase in survival time in patients treated with IL-1RA within the first 2 days if these patients have a 24 per cent or more risk of death within 28 days. There was no benefit if the patient had a risk of death below 24 per cent[136].

Miscellaneous agents

Cytokine synthesis can be blocked at a translational level by steroids and at a pretranslational level by pentoxifylline (oxypentifylline) and amrinone. Steroids block the translation of TNF-α mRNA in macrophages. They must be administered pre-emptively to have an effect;

increases in nitric oxide production can be related to the level of hypotension[87]. Bacterial endotoxin induces iNOS and raised nitric oxide synthesis in venous smooth muscle cells, in the cardiomyocytes and in the endocardium, and leads to increased venous pooling and cardiac dysfunction (sepsis-related dilated cardiomyopathy)[86]. Cytokine induction of myocardial iNOS results in increased nitric oxide production and negative inotropy[88]. NOS activity is significantly higher in patients with sepsis[89].

Studies in animal models on the inhibition of NOS activity have shown a mixed picture of efficacy in the treatment of septic shock[90]. While 30 mg/kg L-nitro-monomethyl arginine will prevent endotoxin shock, 300 mg/kg will accelerate the condition. Early reports suggest that inhibition of nitric oxide is beneficial in septic shock. The benefit of inhibited NOS activity is a sustained increase in systemic blood pressure, while the adverse effects are decreased cardiac output and raised pulmonary vascular resistance[91–94]. Hepatocyte dysfunction appears to be the result of cytokine-induced production of nitric oxide (through iNOS) and cytokine release from macrophages and Kupffer cells[86]. Macrophages synthesize nitric oxide and the high concentrations of nitric oxide are responsible for the cytotoxicity of macrophages to tumour cells and bacteria[84,95]. The cytotoxicity of nitric oxide results from its interaction with iron-containing moieties in enzymes of the respiratory cycle and the DNA synthesis pathways[96].

Reactive oxygen species

Endothelial cells contain xanthine dehydrogenase/oxidase and the free radicals produced or transferred from the extracellular space under normal conditions are reduced by endothelial cell superoxide dismutase, catalase and the glutathione redox cycle. Low intracellular levels of oxygen free radicals stimulate cyclo-oxygenation of arachidonic acid. Superoxide radicals can induce vasodilatation in several tissue beds and this is thought to be mediated by the release of prostacyclin from endothelial cells. However, increased intracellular concentrations of oxygen free radicals are able to inactivate nitric oxide and can inhibit the production of prostacyclin in endothelial cells by inhibiting both cyclo-oxygenase (COX-I) and COX-II synthetases. Higher levels will result in the destruction of these enzymes. In contrast, TXA_2 synthetase is resistant to such free radical inhibition and destruction. The net effect of these interactions is vasoconstriction[97]. In addition, oxygen free radicals can lead to the formation of peroxides and, because of the difference in kinetics between the cyclo-oxygenase and peroxidase enzymes, lipid peroxides can accumulate; raised concentrations of these compounds will also destroy both COX-I and COX-II synthetases. This damage can be prevented by antioxidants. In normal physiology, a balance exists between the production of PGI_2 and TXA_2, and between nitric oxide and oxygen free radicals, which allows for the maintenance of vascular tone[98].

When tissues are injured by ischaemia or anoxia, their ability to control the metabolism of oxygen is compromised and the species that are generated activate a superoxide-dependent chemoattractant process. This leads to an influx of leucocytes which generates still more reactive oxygen species. Reactive oxygen species are involved in most types of inflammatory tissue injury and are derived predominantly from phagocytic leucocytes[99,100]. Reactive oxygen species produce cellular injury directly by oxidative degradation of essential cellular components and indirectly by altering the protease/antiprotease balance that exists between cells. Reactive oxygen species can further initiate and amplify the inflammatory process by upregulation of several proinflammatory cytokines (IL-2, IL-6 and TNF-α) and adhesion molecules (E-selectin, ICAM-1 and VCAM-1)[100,101]. The undisputed contribution of reactive oxygen species to the SIRS has prompted increasing experimental work on means to counteract their local tissue effects[102]. A preliminary report of a randomized trial of *N*-acetylcysteine in patients with established sepsis-induced ARDS suggests that the antioxidant therapy is useful[103].

Platelet activating factor

Endotoxin induces the release of PAF from macrophages, PMNs, platelets and endothelial cells. Systemically, PAF has a negative inotropic effect on the heart and lowers arterial blood pressure. PAF is a potent phospholipid inflammatory mediator that increases cell adhesion, and activates cells by direct effect or through the formation of toxic oxygen species and arachidonic acid metabolites. PAF stimulates the release of TNF-α, leukotrienes, TXA_2, and promotes leucocyte activation and subsequent free radical formation. There is growing evidence that haematological growth factors and cytokines interact with PAF, leading to amplification of mediator release in septic shock, and that PAF mediates many of the toxicities associated with TNF-α and IL-1[104,105]. Within the microcirculation, PAF encourages platelet aggregation, leading to thrombus formation, and markedly alters microvascular permeability by stimulating calcium efflux in endothelial cells, which results in retraction and loss of reciprocal contact. Specific PAF receptor antagonists provide protection against the fatal complications of endotoxic shock in animal models[106,107].

Nutrition

Severe depletion of body protein stores can result from prolonged starvation, or from hormonal or cytokine-mediated effects during critical illness[108–110]. Specialized enteral and parenteral nutrition is now a standard component of care in critically ill patients. This adjunctive therapy corrects and prevents nutrient deficiencies, attenuates the loss of body protein, enhances immune function, and beneficially modifies a body's response to illness, thereby improving clinical outcome in malnourished patients. In patients without severe head injuries, infectious complications are the most common cause of death, and are a frequent cause of morbidity and mortality. Morbidity from sepsis is significantly reduced in critically injured patients when total enteral nutrition (TEN) rather than total parenteral nutrition (TPN) is provided, implying benefits of enteral feeding on host defences[111]. A lack of enteral feeding is thought to lead to a breakdown of the gut mucosal barrier and translocation of bacteria or their products, while the use of TEN or trickle feeding prevents the deterioration in the gut's ability to prevent translocation. Preservation of the barrier function of the gut is essential in controlling sepsis-related morbidity associated with severe injury and stress. Ample experimental evidence suggests that TEN is superior to TPN in preventing many coincidental septic events and modulating the host response to ongoing sepsis that occur in critically ill patients. Immunonutrition is the term being used now to refer to the effects of nutritional 'firm' attachment, in monocyte recruitment occurs with the adhesion of the monocyte integrin $\alpha_m\beta_2$ and the endothelial cell receptor ICAM-1. ICAM-1 can be induced by exposure of the endothelial cells to IL-1, TNF-α and IFN-γ. Monocyte extravasation requires endothelial cells to express monocyte chemoattractant protein (MCP) 1 at the cell to cell junction to allow diapedesis to occur along a chemoattractant gradient[74]. Once inside the intima, the monocytes amplify the MCP-1 signal by synthesizing and secreting their own MCP-1, a characteristic of tissue macrophages[75-77]. Matrix attachment of the extravasated monocytes occurs through integrin receptors and the tissue macrophages express genes for IL-1, IL-8 and superoxide dismutase[78,79].

Monocytes/macrophages carry out the fundamental protective functions of ingesting and killing invading micro-organisms. Macrophages play a central role in the immune response by presenting antigens to lymphocytes during the development of specific immunity. Migration of monocytes into different tissues appears to be a random phenomenon during homeostasis, where they undergo transformation into tissue macrophages with morphological and sometimes functional properties that are characteristic for that tissue. The life span of tissue macrophages is believed to be months. The most important functional step in the maturation of bone marrow-derived monocytes to tissue macrophages is the lymphokine-driven conversion of the normal resting macrophage to an activated macrophage[80]. These cells are generally larger, more metabolically active, and able to release soluble substances and oxidative metabolites. Activated macrophages migrate more vigorously in response to chemotactic factors released from invading micro-organisms and enter sites of inflammation more efficiently than unactivated macrophages. Although tissue macrophages are capable of phagocytosis, tissue macrophage-mediated modulation and chemoattraction of non-macrophage inflammatory cells are important activities during sepsis[81]. Once activated, macrophages are the source of numerous cytokines involved in host defence and inflammation. Activation of tissue macrophages results in the generation of reactive oxygen species, and oxidation of arachidonic acid by lipo-oxygenase and cyclo-oxygenase pathways to generate leukotrienes, prostaglandins and thromboxane. Monocytes and tissue macrophages phagocytize particulate material via at least two distinct receptors present in their plasma membrane: the immunoglobulin (Ig) G Fc receptor and the receptor for the alternate complement pathway. Phagocytosis is increased by the presence of C3B. Particles opsonized with C3b react with activated mononuclear phagocyte C3b adherence receptors to promote increased phagocytosis through the Fc and C3b receptors respectively. Phagocytosis is augmented by fibronectin.

Secondary inflammatory mediators

Arachidonic metabolites

Metabolites of arachidonic acid, particularly those of lipo-oxygenase and cyclo-oxygenase, are significant autocrine and paracrine mediators of the SIRS. Recognized early as potent vasodilators, they play an important role in the low systemic vascular resistance and hypotension that occur in septic shock. LPS, TNF-α and IL-1 all induce the release of prostaglandins from endothelial cells. The major endothelial cell-derived prostaglandin is PGI_2, a potent vasodilator. Raised PGI_2 concentrations have been found to correlate with the severity of septic shock. The abluminal release from endothelial cells is small compared with its luminal release. PGI_2 acts on smooth muscle cells via receptor-mediated activation of adenylate cyclase. The ratio of PGI_2/PGE_2 generation is lower in the microcirculation than in major vessels. With PGI_2 production, endothelial cells also generate a small amount of TXA_2, a proaggregating vasoconstrictor. A variety of other eicosanoids, such as monohydroxy, dihydroxy and epoxy derivatives of arachidonic acid, which are formed by the cyclo-oxygenase-, lipo-oxygenase- and cytochrome P450-dependent mono-oxygenation pathways, also influence vascular tone. PGI_2 inhibits platelet aggregation and adhesion, reduces thrombus formation and acts synergistically with prostaglandin PGE_2 to increase the effects of serotonin and bradykinin. PGE_2 inhibits both IL-1 production and responsiveness of thymocytes to IL-1. Low concentrations of PGE_2 stimulate TNF-α release, while higher concentrations suppress TNF-α production at a dose-dependent level; PGE_2 inhibits mitogenesis of T and B cells and acts synergistically with prostacyclin to increase the effects of serotonin and bradykinin on vascular permeability. TXA_2 induces platelet aggregation and neutrophil accumulation, increases vascular permeability and enhances permeability of single and double unit membranes. LTB_4 promotes neutrophil chemotaxis and adhesion of neutrophils to endothelium. Neutrophils have specific LTB_4 receptors. LTB_4 is weakly chemotactic for eosinophils and increases vascular permeability, either directly or through interaction with neutrophils and endothelial cells. LTC_4, LTD_4 and LTE_4 stimulate release of prostacyclin, increase vascular permeability and cause contraction of adjacent endothelial cells and a resulting increase in the diameter of interendothelial cell pores.

Nitric oxide

Synthesis of nitric oxide plays a crucial role in acute and chronic inflammatory processes, in the SIRS and in sepsis[82,83]. Nitric oxide is synthesized from the conversion of L-arginine to citrulline by at least two categories of enzyme: constitutive nitric oxide synthases (cNOS; predominantly membrane bound) and inducible nitric oxide synthases (iNOS; predominantly cytosolic) both of which are calcium- and calmodulin-dependent. Protein phosphorylation by the guanosine 3',5'-cyclic monophosphate (cGMP)-dependent kinases, which are activated by nitric oxide-mediated increases in target cell cGMP, is the basis of many of the effects attributed to nitric oxide. Nitric oxide shares many of the vasoactive properties of prostacyclin in that it can relax smooth muscle and inhibit platelet aggregation. In the appropriate circumstances, nitric oxide can be converted in the endothelial cell to peroxynitrite, a potentially toxic molecule. Peripheral blood monocytes, alveolar macrophages, Kupffer cells and neutrophils, once stimulated, are all capable of synthesizing iNOS and producing nitric oxide[84]. Nitric oxide enhances the vasodilatation, the formation of oedema and the modulation of sensory nerve endings which are hallmarks of the inflammatory response. Inhibition of nitric oxide synthesis will reduce the degree of acute inflammation. Raised concentrations of nitric oxide are likely to come from a combination of sources: activated vascular cells, neutrophils and macrophages[85,86]. These effects can be prevented by treatment with glucocorticoids and NOS inhibitors. In endotoxic shock,

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Surgical workshop

Specimen retrieval in laparoscopic cholecystectomy

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Extraction of the gallbladder after laparoscopic cholecystectomy presents a risk of peritoneal wound contamination. To avoid potential problems use of specimen retrieval bags has been advocated[1]. A method of gallbladder extraction is described which is simple and cheap.

Surgical technique

A sterile, size 6 hypoallergenic powderless surgical glove with a thickened or rolled cuff is used. The glove is twisted at the base of the palm, and securely stitch-tied at this level with a 1/0 silk transfixion stitch, much like a herniotomy. The fingers and glove 1 cm distal to the tie are cut off and discarded. The silk threads on the tie are left 2 cm long. This creates a conical receptacle, the mouth of which has a tendency to remain open because of the cuff of the glove (*Fig. 1*).

The silk threads are grasped with a pair of laparoscopic forceps and driven through the 10-mm epigastric port. The bag is then positioned, under vision, in the Rutherford Morison pouch, with its open mouth facing the gallbladder. The gallbladder and any stones are then easily placed into the receptacle. To remove the bag, a pair of toothed laparoscopic forceps, via the umbilical port, is applied across the diameter of the open mouth of the glove. With the camera in the 10-mm epigastric port, the forceps is withdrawn into the umbilical port, bringing the cuff of the glove into the sleeve (*Fig. 2*). The umbilical port is then slowly removed. The mouth of the glove can be brought out on to the surface, leaving the wound completely protected. This then allows removal of the bag and contents.

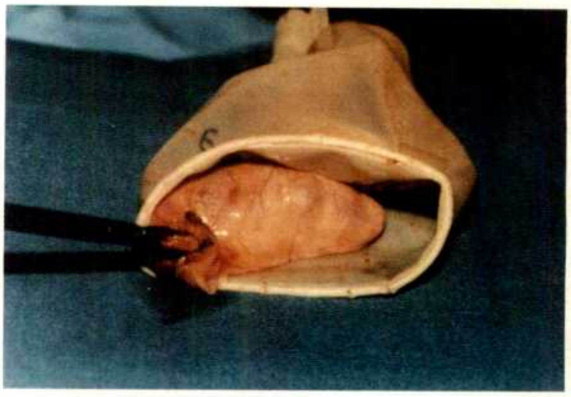
Fig. 1 A prepared glove (containing specimen) demonstrating its open mouth

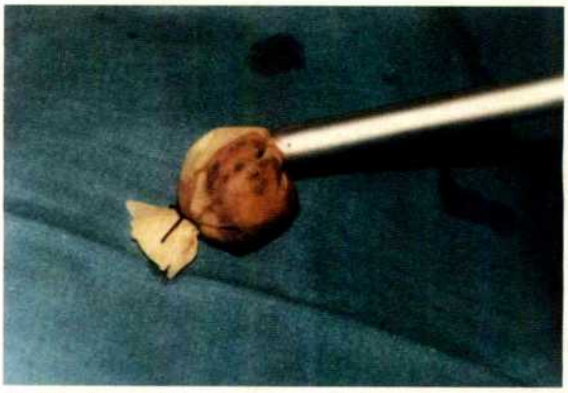
Fig. 2 The glove and specimen are withdrawn into the sleeve of the umbilical port before extraction from the abdomen

Discussion

The glove used is sterile, hypoallergenic and powderless, thereby eliminating foreign body introduction and potential adhesion formation.

Safety is enhanced by the prevention of intraperitoneal and wound contamination. Perforation of the gallbladder as it is being withdrawn, with contamination of the peritoneal cavity and wound with bacteria, gallstones and sometimes malignant cells may have a serious impact on operative outcome[1-3]. Perhaps only 40 per cent of gallbladder tumours are suspected at the time of surgery[4].

If the gallbladder is perforated during cholecystectomy, the placement of the open necked glove in the abdomen allows easy harvest of gallstones into the bag as they present, thereby reducing fiddlesome manoeuvring inside the abdomen, as well as avoiding the need for repeated removal of instruments.

The method is safe, cheap, simple and potentially reduces significant morbidity. Its routine use at laparoscopic cholecystectomy is strongly advocated where bile leak occurs or tumour is suspected.

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Outpatient laparoscopic cholecystectomy

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Introduction The results of laparoscopic cholecystectomy performed as an outpatient procedure were evaluated in a prospective study.

Methods Initially, only well motivated and healthy patients were offered outpatient laparoscopic cholecystectomy. After 50 procedures, all patients referred to the hospital, except those with American Society of Anesthesiologists (ASA) grade IV and those living alone, were included. Some 200 procedures were studied.

Results Twelve patients (6 per cent) were admitted, and 188 (94 per cent) were discharged 4–8 h after operation. Fifteen patients (8 per cent) who had early discharge were readmitted, nine with complications; in six no complications were documented. The frequency of minor complications was 2 per cent and of major complications 5 per cent. Some 173 patients who had successful outpatient laparoscopic cholecystectomy completed a questionnaire: 164 (95 per cent) characterized their experience as excellent, five (3 per cent) as good, two (1 per cent) as intermediate and two (1 per cent) as unacceptable.

Discussion This high achievement of day-case treatment, even in patients with ASA grade III, is explained by a new anaesthetic regimen together with good surgical technique and close follow-up.

Postoperative discomfort is significantly reduced in patients who have laparoscopic cholecystectomy rather than open surgery[1-5]. However, the authors' experience in advance of the present study was that patients having laparoscopic cholecystectomy often need postoperative opiate analgesics, and that nausea is frequent, making same-day discharge difficult. The safety of same-day laparoscopic cholecystectomy has been questioned, mainly due to the significant postoperative reduction of pulmonary vital capacity and high analgesic requirements[6]. Morbidity and mortality rates may be higher following same-day laparoscopic cholecystectomy[7]. Safety seems to depend on the methods of anaesthesia and surgery. A new anaesthetic regimen was used in the present study, and the most experienced laparoscopic surgeons performed or supervised all operations. The aims of the study were to describe complication rates of this method of ambulatory laparoscopic cholecystectomy and to record when and how complications presented. A questionnaire was used to assess patient tolerance of day-case laparoscopic cholecystectomy.

Patients and methods

Patients treated in the Department of Ambulatory Surgery between January 1994 and December 1995 were included. Two days in advance of surgery patients were seen for preadmission and liver function testing. Selection of patients for preoperative endoscopic retrograde cholangiopancreatography (ERCP) was based on a discriminant analysis function including estimation of serum bilirubin, aspartate aminotransferase (ASAT) and γ-glutamyl transpeptidase (GT) levels together with patient age[8].

Patient selection

The first 50 patients selected were those with American Society of Anesthesiologists (ASA)[9] grades I and II; the next 150 patients included those with ASA grade III. Patients living alone and those with severe psychiatric disorders were excluded. Only elective cases were included, but no effort was made to avoid difficult gallbladders. *Table 1* shows the profile of the 200 patients.

Premedication and anaesthetic regimen

All patients were admitted at 07.00 hours on the day of operation. An intravenous cannula was inserted 30 min before operation and 1–3 mg midazolam was given intravenously. Prophylaxis against postoperative pain and nausea was achieved with ketorolac 30 mg, ketamine 15 mg and ondansetron 4 mg given intravenously before the start of anaesthesia, which was initiated by fentanyl 0·1–0·2 mg and propofol 1·5–2·0 mg kg^{-1}. During induction, vecuronium 0·1 mg kg^{-1}, a medium long-acting muscle relaxant, was given. Some 3 min later, endotracheal intubation was performed. Anaesthesia was maintained by propofol infusion 10 $\text{mg kg}^{-1}\,\text{h}^{-1}$ during the first 10 min, and thereafter 8 $\text{mg kg}^{-1}\,\text{h}^{-1}$. Analgesia was provided by alfentanil 0·5–1·0 mg intravenously when needed. The degree of muscle relaxation was controlled by nerve stimulation. At the end of the surgical procedure, patients were reversed with neostigmine 2·5 mg and glycopyrrolate 0·5 mg.

Surgical procedure

The standard procedure was two 10-mm ports in the midline and two 5-mm ports on the right side. The surgeon stood on the patient's right side, with the patient supine. A senior laparoscopic surgeon participated in each operation. Intraoperative cholangiography was not used. At the end of each procedure, 0·5 per cent bupivacaine was infiltrated into each trocar site.

Table 1 Patient characteristics

Median (range) age (years)	49 (17–82)
Sex ratio (M:F)	42:158
ASA grade	
I	150
II	44
III	6
Median (95 per cent confidence interval) body mass index	27·8 (22·8–42·5)

ASA, American Society of Anesthesiologists

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Postoperative care

Immediately after surgery paracetamol 1 g was given rectally. Thereafter, small doses of opiate were given intravenously when needed. Postoperative pain observed more than 2 h after operation was treated by codeine and/or paracetamol in combination. When the patients left the day-care department 4–8 h after operation, they took 20 codeine–paracetamol tablets with them. When postoperative nausea had to be treated in the department, metoclopramide 10 mg was given intravenously up to two times as first choice, supplemented by haloperidol 2·5 mg and/or ondansetron 4 mg intravenously if needed. Full information sheets, including contact numbers, were given to all patients on discharge.

Postoperative pain, sickness and patient satisfaction

Postoperative pain, sickness and analgesic use were registered over two intervals: from 0 to 6 h and from 6 to 24 h after operation. A visual analogue scale was used for both parameters. Data were collected at the bedside during the first interval. On the first postoperative day, one of the anaesthetists associated with the project contacted each patient by telephone. Three months after surgery all patients had a consultation in the surgical outpatient department, when the final assessment of postoperative complications was performed and patient satisfaction data for all 200 patients were collected.

Classification of complications

The Toronto classification system was used to define complications as follows[10]: grade 1, not life threatening and never associated with a hospital stay greater than twice the median stay for the uncomplicated procedure; grade 2, potentially life threatening, resulting in a hospital stay more than twice the median stay for the uncomplicated procedure, but not resulting in residual disability; grade 3, any complication with residual disability; and grade 4, death of the patient as a result of a complication. The authors' adaptation of this classification system has been described previously[5].

Statistical analysis

Values are given as median (range or 95 per cent confidence interval). Null hypotheses of no differences between groups have been tested by Kruskal–Wallis non-parametric analysis of variance[11].

Results

Of the 200 patients, 188 (94 per cent) were discharged 4–8 h after operation. Twelve patients (6 per cent) were admitted (*Table 2*). They were all discharged after an uneventful course: four patients after overnight observation, seven stayed between 2 and 5 days, and one patient stayed for 8 days in hospital, after a converted procedure for a tumour of the appendix (adenocarcinoma), which was treated by right hemicolectomy. Neither of the patients with gallbladder empyema had clinical signs suggesting the diagnosis before operation. The patient admitted because of depression was a refugee whose social situation altered after inclusion in the study.

Table 2 Main reason for primary admission

	No. of patients	Main treatment
Conversion to open surgery	4	Observation
Gallbladder empyema	2	Antibiotics
Postoperative ERCP necessary	2	Observation after ERCP
Nausea and/or pain	2	Analgesia
Vasovagal reflex	1	Observation
Depression	1	Observation

ERCP, endoscopic retrograde cholangiopancreatography

A further 15 patients (8 per cent) were readmitted after 1–53 days (*Table 3*). The most frequent reason for readmission was residual common bile duct (CBD) stones, all successfully removed by endoscopic sphincterotomy. One of these patients also had a laparotomy for bile leak, and was treated for 5 days in the intensive care unit for sepsis. In two other patients liver function tests suggested CBD obstruction, but ERCP revealed no stone. Two patients were readmitted with CBD injury. One young patient with a very gracile hepatic duct suffered a 'tent injury'. The other common duct injury was a small side-hole caused by diathermy in a patient with severe chronic cholecystitis.

Complications, which needed immediate treatment, were the reason for nine of 15 readmissions (*Table 3*). Overall complications included three (2 per cent) of grade 1 (one wound infection and two wound haematomas) and ten (5 per cent) of grade 2 (the previously mentioned two CBD injuries, one incisional hernia and seven retained bile duct calculi, four of which presented with bile leak). All patients except those with wound haematomas presented later than the first postoperative day.

Postoperative pain, nausea and patient satisfaction

Severe nausea or pain during the first 6 h was infrequent (*Table 4*). Some 167 patients (84 per cent) had no or mild to moderate pain; 190 (95 per cent) had no or mild to moderate nausea. Opiate treatment during the first 6 h was needed by only 43 patients (22 per cent); the highest

Table 3 Main reason for readmission

Diagnosis	No. of patients	Main investigation or treatment
Residual CBD stone	7	Successful stone removal after ES
CBD injury	2	CBD stent after ES (1) Reoperation, clip removal (1)
Pathological liver function test results	2	ERCP and observation
No pathology	2	Observation
Viral infection	1	Observation
Constipation	1	Observation

CBD, common bile duct; ES, endoscopic sphincterotomy; ERCP, endoscopic retrograde cholangiopancreatography

Table 4 Postoperative pain and nausea in the first 24 h after operation

	Time after operation (h)			
	0–6		6–24	
	Pain	Nausea	Pain	Nausea
None	55	130	21	108
Mild to moderate	112	60	112	34
Severe	26	3	16	7
Unknown	7	7	51	51

Table 5 Possible indicators of primary admission in each group

	Admission ($n = 12$)	Readmission ($n = 15$)	Successful same-day surgery ($n = 173$)
Median operating time (min)	55 (25–200)	50 (28–178)	57 (23–190)
Median age (years)	50 (21–67)	43 (17–74)	48 (19–82)
Percentage with ASA grade I	72	78	75

Values in parentheses are 95 per cent confidence intervals. ASA, American Society of Anesthesiologists. Comparison of the three groups by Kruskal–Wallis non-parametric analysis of variance showed no significant differences

dose was for ketobemidone 5 mg. During the first 24 postoperative hours, pain was a severe problem for 16 patients (8 per cent). During the control consultation 3 months later, 95 per cent of 173 patients who avoided readmission after successful ambulatory laparoscopic cholecystectomy were very satisfied, 3 per cent characterized their experience as good, 1 per cent as intermediate, and only 1 per cent described their experience as unacceptable; however, none had contacted the surgical department despite severe pain on the first postoperative day. Among the 27 admitted or readmitted patients, only four characterized the treatment as excellent, 15 as good, six as intermediate and two as unacceptable.

For the first 50 patients, excluding those with ASA grade III, the rate of successful ambulatory laparoscopic cholecystectomy was 92 per cent, increasing to 95 per cent for the following 150 cases. No patient with ASA grade III was admitted or readmitted. Median operating time differed by less than 15 per cent among admitted, readmitted and successfully discharged patients (*Table 5*). Neither age nor previous health (measured as the percentage with ASA grade I) differed significantly between the groups (*Table 5*).

Discussion

The feasibility of ambulatory laparoscopic cholecystectomy was high in the present series. Only 14 per cent had to be treated as inpatients. Among the rest, nearly all were satisfied, experiencing less postoperative pain and discomfort than they had expected. Only 1 per cent would refuse an outpatient operation if they were to be treated again. Serious complications were comparable to those in the authors' previous inpatient series[5], but all were recognized and treated rapidly, and life-threatening conditions were never observed, owing to close follow-up. Of the 27 admitted and readmitted patients, nearly one-third were dissatisfied. The most frequent reason for readmission was a grade 2 complication, and it is unlikely that inpatient care would have improved this outcome.

The reduced postoperative nausea, pain and fatigue was due to the improved anaesthetic regimen. Nitrous oxide was not used, and antiemetic prophylaxis by ondansetron was added. This reduced the frequency of postoperative nausea from the usual 40–60 per cent[12] to the present 33 per cent. The non-steroidal anti-inflammatory drug ketorolac[13], together with a small dose of ketamine, seemed to reduce postoperative pain[14] and made it possible to avoid long-acting opioids during and after operation. This is the principal difference from the authors' of laparoscopic cholecystectomy, when patients needed at least 24 h postoperative recovery.

Patients with grade 2 complications in the present series did not experience severe pain or nausea within the first 24 h. As complications cannot be predicted at discharge, information about possible complications must be clearly instructed to, and understood by, each patient.

Reduced pulmonary vital capacity has been described after laparoscopic cholecystectomy[6]. Pulmonary capacity was not recorded in this study, but pulse oximetry and estimation of end-tidal partial pressure of carbon dioxide revealed no abnormalities that could have generated admission. During postoperative follow-up, none of the patients experienced any respiratory problems. The present success rates are high, compared with those of several earlier reports[15–21], but the primary discharge rate of 80–90 per cent of patients after outpatient laparoscopic cholecystectomy has been published previously[22,23]. Advanced age, major associated health problems and long operation have been described as indications for hospital admission[21]. In the present series, all these criteria were equally distributed in success and failure groups (*Table 5*), but few patients were admitted and the corresponding statistical power was very low.

The importance of safe surgical technique in outpatient laparoscopic cholecystectomy has been emphasized[24] and this should include the possibility of performing intraoperative cholangiography. The present complications (one 'tent injury', one diathermy burn in the CBD, plus seven residual bile duct stones) can be interpreted as arguments in favour of routine intraoperative cholangiography. A better prediction of CBD stones was obtained by slightly different indicators in the authors' previous series[4,5]. In the present study, the patients (4 per cent) with residual stones had either normal liver function test results or slightly raised ASAT concentration.

The estimated average extent of same-day surgery in Norway is 24 per cent of all surgical procedures[25], lower than that in many European countries[26]. People living in a city, at least, could be offered same-day laparoscopic cholecystectomy. The development of outpatient laparoscopic cholecystectomy in this hospital has eliminated the waiting list, with clear advantages to patients and hospital economy. Laparoscopic cholecystectomy performed as an outpatient procedure with close postoperative follow-up is the best and most cost-effective treatment for symptomatic gallstones.

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Thromboembolism prophylaxis during laparoscopic cholecystectomy

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Background The aim of this study was to determine current UK practice with regard to thromboembolism prophylaxis during laparoscopic cholecystectomy.

Methods Postal questionnaires were sent to 800 members of the Association of Surgeons; replies were received from 551 surgeons (69 per cent) of whom 417 practised laparoscopic cholecystectomy.

Results Heparin was prescribed to all patients by 74 per cent, and selectively by 20 per cent, of respondents. Surgeons who performed fewer than ten laparoscopic cholecystectomies per annum were significantly less likely to use heparin ($P < 0.001$) and more likely to believe that heparin produces significant adverse bleeding ($P < 0.01$). Thirty per cent of respondents used low molecular weight heparin. Stockings to deter thromboembolism were used by 74 per cent, and pneumatic compression by 37 per cent. Indications for heparin varied considerably and were not influenced by Thromboembolic Risk Factors (THRIFT) guidelines. Only 20 per cent of respondents considered that thromboembolism was a problem; 91 per cent reported that they had never experienced a thromboembolic complication following laparoscopic cholecystectomy.

Conclusion The rate of thromboembolism after laparoscopic cholecystectomy is unknown but most surgeons believe the risk is very low. Surgeons' attitudes towards thromboembolism prophylaxis are variable, but most experienced surgeons use low-dose heparin.

Patients having abdominal surgery are at risk of thromboembolism because of procoagulant rheological changes accompanying the 'surgical stress response'[1] and because of immobility leading to venous stasis. Minimally invasive techniques, such as laparoscopic cholecystectomy, might be expected to lower the risk of thromboembolism because of reduced surgical stress and earlier mobilization[2,3]. However, the increase in intra-abdominal pressure from pneumoperitoneum[4], together with a head-up operating position, impedes venous return, leading to venous pooling in the legs[5,6]. The laparoscopic approach might therefore increase the risk of deep venous thrombosis (DVT) and subsequent pulmonary embolism, but few studies have addressed this area[7,8].

Individual surgeons have formulated a thromboembolism prophylaxis policy in the absence of scientific data[9]. The aim of this study was to determine how UK surgeons gauge the risk of thromboembolism and to discover what methods they employ to minimize the risk of DVT and/or pulmonary embolism after laparoscopic cholecystectomy.

Materials and methods

Postal questionnaires were sent to 800 members of the Association of Surgeons of Great Britain and Ireland. Surgeons were asked how many laparoscopic cholecystectomies they performed per annum and to supply details of which method of thromboembolism prophylaxis, if any, was employed. They were also asked questions about how they perceived the risk of thromboembolism after laparoscopic cholecystectomy and how many thromboembolic complications following the procedure they had encountered personally. Some 6 weeks after the last questionnaire had been posted, 551 replies (response rate 69 per cent) had been received. Of respondents, 417 (76 per cent) practised laparoscopic cholecystectomy, and this group forms the basis of the present report.

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Results

Heparin was the most popular form of thromboembolism prophylaxis. Surgeons who performed fewer than ten laparoscopic cholecystectomies per annum were significantly less likely to use heparin ($P < 0.001$) and were more likely to express the view that heparin would cause adverse intraoperative bleeding ($P < 0.01$, Fisher's exact test). Thirty per cent of respondents used low molecular weight heparin (LMWH), but this did not relate significantly to activity. Several respondents would prefer to use LMWH but were not doing so for financial reasons. Stockings to deter thromboembolism were used by 74 per cent, and some form of pneumatic compression device by 37 per cent of respondents (*Table 1*). Only seven surgeons used no thromboembolism prophylaxis at all. Surgeons who prescribed heparin selectively had considerable variation in the criteria they used (*Table 2*). Only one-third of respondents considered that conversion to open cholecystectomy and/or emergency operation for acute cholecystitis and/or pancreatitis was an indication for heparin prophylaxis.

Median postoperative stay was 2 (range 0–6) days. Surgeons who performed more than 25 procedures per year were significantly more likely to discharge patients within 2 days ($P < 0.003$, Fisher's exact test) (*Table 3*). There was no significant relationship between postoperative stay and the use of thromboembolism prophylaxis, suggesting that time to mobilization and discharge did not influence policy.

Only 20 per cent of respondents considered that thromboembolism was a problem following laparoscopic cholecystectomy; 91 per cent had never experienced a thromboembolic complication following the procedure. Surgeons who performed more than 25 procedures per annum were significantly more likely to have seen a thromboembolic complication ($P < 0.02$, Fisher's exact test). The perceived low incidence of thromboembolism may, at least in part, reflect low throughput.

Table 1 Thromboembolism prophylaxis during laparoscopic cholecystectomy

	No. of procedures performed per annum				
	< 10	10–25	26–50	> 50	Total
No. of surgeons	15 (4)	103 (25)	149 (36)	150 (36)	417 (100)
Which patients do you prescribe subcutaneous heparin to?					
All	8 (53)	81 (79)	111 (74)	110 (74)	310 (74)
Some	4 (27)	17 (16)	32 (22)	32 (21)	85 (21)
None	3 (25)*	5 (5)	6 (4)	8 (5)	22 (5)
Do you use low molecular weight heparin? (Yes:No)	3 (20):12	34 (33):69	46 (31):103	44 (29):106	127 (30):268
When do you give your first dose of heparin?					
Before operation	7	79	126	123	335 (85)
At induction	5	16	16	18	55 (14)
After operation		3	1	1	5 (1)
Do you use thromboembolism-deterrent stockings? (Yes:No)	8 (53):7	69 (67):34	111 (74):38	119 (79):31	307 (74):110
Do you use dextran? (Yes:No)	0 (0):15	2 (2):101	0 (0):149	2 (1):148	4 (1):413
Do you use pneumatic compression devices? (Yes:No)	6 (40):9	34 (33):69	59 (40):90	54 (36):96	153 (37):264
What dose of standard heparin do you use?					
5000 units at induction only		3	9	9	21 (8)
5000 units twice daily	7	54	78	82	221 (82)
5000 units three times daily	2	7	11	6	25 (9)
5000 units four times daily				1	1 (1)

Values in parentheses are percentages. $^*P < 0.001$ (two-tailed Fisher's exact test)

Table 2 Indications for selective use of heparin as thromboembolism prophylaxis during laparoscopic cholecystectomy

	No. of procedures performed per annum				
	< 10 ($n = 4$)	10–25 ($n = 17$)	26–50 ($n = 32$)	> 50 ($n = 32$)	Total ($n = 85$)
Age (years)					
> 40	1	9	17	15	42 (49)
> 60	3	13	20	21	57 (67)
Obesity	3	15	20	26	64 (75)
Varicose veins	1	9	18	13	41 (48)
Oral contraceptive pill	2	14	25	25	66 (78)
Previous deep vein thrombosis and/or pulmonary embolism	4	17	31	32	84 (99)
Known thrombophilia	2	14	27	29	72 (85)
Operation lasting over 1 h	2	3	6	8	19 (22)
Conversion to open cholecystectomy	1	6	11	14	32 (38)
Operation for acute cholecystitis	1	4	9	13	27 (32)
Operation for pancreatitis	1	4	7	11	23 (27)

Values are number of surgeons believing a particular factor to be an indication for heparin. Values in parentheses are percentages

Discussion

The Thromboembolic Risk Factors (THRIFT) Consensus Group concluded that thromboembolism remains a common cause of morbidity and mortality following abdominal operations and advised routine prophylaxis for patients at moderate to high risk[10]. Mechanical methods such as stockings to deter thromboembolism and various pneumatic compression devices are popular but, unlike heparin, have not been shown to reduce fatal pulmonary embolism. In the present study heparin was the most common form of prophylaxis. Although randomized controlled studies indicate that low-dose heparin does not increase bleeding after open surgery, 10 per cent of respondents considered that heparin would cause adverse bleeding during laparoscopic cholecystectomy[11]. This view was more commonly held by surgeons who performed fewer than ten procedures per year. The indications for selective prescription of heparin were not influenced by THRIFT guidelines.

One argument for not using routine prophylaxis is that patients who have laparoscopic cholecystectomy mobilize earlier, and mount a smaller stress response, than after open cholecystectomy[12,13]. Although the median duration of postoperative stay in this study was 2 days, there was no significant relationship between hospital stay and thromboembolism prophylaxis. Surgeons who performed more than 25 laparoscopic cholecystectomies per year were more likely to discharge patients within 2 days and to use heparin routinely.

Table 3 Length of hospital stay and perceptions of thromboembolic risk during laparoscopic cholecystectomy

	No. of procedures performed per annum				
	< 10 ($n = 15$)	10–25 ($n = 103$)	26–50 ($n = 149$)	> 50 ($n = 150$)	Total ($n = 417$)
How long do most of your patients having laparoscopic cholecystectomy stay in hospital after operation? (days)					
1	3	32	52	69	156 (37)
1–2	1	21	36	36	94 (23)
2	3	39	48	36	126 (30)
2–3	4	4	9	7	24 (6)
3	3	6	3	2	14 (3)
3–4	1				1 (0)
4		1			1 (0)
6			1		1 (0)
Do you think administering heparin increases the risk of clinically significant bleeding? (Yes:No)	5 (33)*:10	8 (8):95	15 (10):134	13 (9):137	41 (10):376
Do you perceive DVT and pulmonary embolism as a problem in your patients undergoing laparoscopic cholecystectomy? (Yes:No)	3 (20):12	25 (24):78	27 (18):122	28 (19):122	83 (20):334
How many DVTs or pulmonary embolisms have you seen in patients undergoing laparoscopic cholecystectomy?					
None	14	97	138	131	380 (91)
1	0	5	7	11	23 (6)
2	1	1	3	7	12 (3)
3	0	0	0	1	1 (0)
4	0	0	0	0	0 (0)
5	0	0	1	0	1 (0)

Values in parentheses are percentages. DVT, deep vein thrombosis. *$P < 0{\cdot}01$ (surgeons who performed ten or fewer operations per year were more likely to believe that heparin caused bleeding) (two-tailed Fisher's exact test)

The risk of thromboembolism following laparoscopic surgery has not yet been defined and there are clear differences in practice among UK surgeons. Many surgeons do not use proven methods of prophylaxis during laparoscopic cholecystectomy, even in patients at moderate or high risk as defined by the THRIFT group. Furthermore, many do not perceive thromboembolism as a problem; the majority have never experienced a thromboembolic complication following laparoscopic cholecystectomy. The question that remains to be answered by properly conducted studies is whether this clinical perception is accurate and whether the current attitudes to thromboembolism prophylaxis during laparoscopic cholecystectomy are appropriate.

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Surgical management of pancreatic necrosis presenting with locoregional complications

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Background Local complications of pancreatic necrosis may occur after surgery, but when they occur spontaneously render surgical treatment more hazardous and impair prognosis.

Methods A retrospective review was carried out of 83 patients who underwent surgery for pancreatic necrosis from 1988 to 1995, to determine the incidence, type, treatment and outcome of locoregional complications caused by pancreatic necrosis associated with acute pancreatitis.

Results Seventeen patients (20 per cent) were identified to have intra-abdominal complications with pancreatic necrosis either before operation or at the time of surgery. The majority of patients had a delay in intervention (mean 46 days). At presentation ten of the 17 patients had one or more organ system failures. Fourteen patients had gastrointestinal tract involvement, two had involvement of the biliary tract and one patient had a splenic rupture. Six patients died.

Conclusions In patients with pancreatic necrosis, development of locoregional complications is associated with a high mortality rate. The presence of gastrointestinal bleeding, peritonitis, jaundice or pneumoperitoneum in such patients suggests the presence of a complication of the necrotic process and should prompt early intervention. Early referral of patients with severe acute pancreatitis to specialized units may reduce the risk of locoregional complications.

Locoregional complications in a majority of patients with pancreatic necrosis have been reported to occur after operation as a result of trauma sustained at the time of initial necrosectomy or re-exploration, or because of pressure necrosis caused by abdominal drains[1–4]. Most of these complications can be managed conservatively. However, complications may also result from erosion by the necrotic process itself; these manifest before operation or are recognized at the time of surgery. The presence of such complications renders the entire surgical procedure more complex and adversely affects outcome. This article reviews an experience with the locoregional complications of pancreatic necrosis. The incidence, spectrum, presentation, management and outcome were studied.

Patients and methods

Over a period of 8 years (1988–1995), 83 patients with infected pancreatic necrosis were managed in this department and in 17 (20 per cent) of these an intra-abdominal complication related directly to the necrotic process was identified. The presence of necrosis was confirmed by contrast-enhanced computed tomography (CT) and infection was suggested by culture of fluid obtained by guided aspiration from the area of necrosis with clinical evidence of sepsis. The records of these patients were reviewed. The presence of organ system failure (OSF) was evaluated according to the criteria described by Tran and Cuesta[5]. After adequate resuscitation patients underwent surgery. Necrosectomy, drainage of the residual cavity by large bore catheters and creation of a tube jejunostomy for feeding was the standard procedure. Cholecystectomy was done in patients with gallstones. After operation the drains were irrigated with isotonic saline until the effluent was clear, using a mean volume of 6 (range 2–10) litres, for a mean of 9 (range 5–18) days. Reoperation was performed in the presence of persistent or recurrent sepsis, i.e. fever greater than 38°C for more than 3 days, persistent pulse rate more than 120 per min up to the third postoperative day, leucocytosis exceeding 10 000 per mm^3 beyond the third postoperative day and CT showing residual or new collections in the abdomen.

Statistical significance was determined by Student's t test and normal distribution test.

Results

There were 12 men and five women, with complications of pancreatic necrosis. The mean age was 46 (range 26–74) years. Acute pancreatitis was gallstone induced in ten patients and seven patients had a history of alcoholism. Fourteen patients were referred from peripheral hospitals 26–53 (mean 41) days after the onset of pancreatitis, while three patients were admitted with the diagnosis of acute pancreatitis that progressed to the stage of necrosis in this hospital. None of these patients had undergone intra-abdominal surgery in the recent past.

At presentation, three patients had history of haematemesis, one patient each had gastric outlet obstruction, jaundice and melaena. Abdominal examination revealed peritonitis in four patients and one patient came with abdominal distension and shock. Ten patients had OSF; four had single organ dysfunction, five had two, and one had three failed organs or systems. Renal and pulmonary failure were the commonest. In contrast, of the 66 patients with no local complication of the necrotic process, only 12 (18 per cent) had OSF at the time of admission ($P < 0{\cdot}01$). Chest radiography in two patients showed pneumoperitoneum. Contrast-enhanced CT showed the presence of pancreatic necrosis and extensive extrapancreatic necrosis. Upper gastrointestinal endoscopy in three patients with haematemesis revealed bleeding from the medial wall of the duodenum in two patients and from the posterior wall of the stomach in one. In the patient with gastric outlet obstruction, barium meal examination showed an irregular filling defect in the pyloric antrum and duodenum with a perforation in the

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first part of duodenum (*Fig. 1*). Abdominal paracentesis in four patients with peritonitis yielded foul smelling haemorrhagic fluid in two patients and bile-stained fluid in two. The organisms grown from the fluid included *Escherichia coli* (three patients), *Klebsiella pneumoniae* (two patients) and *Streptococcus faecalis* (one patient).

All patients underwent emergency laparotomy. The mean interval between the onset of pancreatitis and surgical intervention was 46 (range 18–57) days, whereas in the 66 patients with no complication, the mean interval was 29 (range 16–41) days ($P < 0.05$). The indication for surgery in the latter group was the presence of sepsis and lack of improvement despite 48–72 h of management in the intensive care unit. Preoperative fine needle aspiration was done in 40 of the 83 patients (48 per cent) and showed infection in all of them. In the remaining patients, the presence of infection was confirmed by culture of pus and necrotic tissue taken at the time of necrosectomy. At surgery, extensive pancreatic and peripancreatic infected necrosis was seen in all patients. The complications encountered are listed in *Table 1*.

After operation 14 patients needed respiratory support for a period ranging from 18 h to 19 days. Two patients underwent haemodialysis for rising serum creatinine and hyperkalaemia. Four patients had stress-induced upper gastrointestinal bleeding and three had bleeding from the drains; all were managed conservatively. Four of the 17 patients needed re-exploration because of persistent

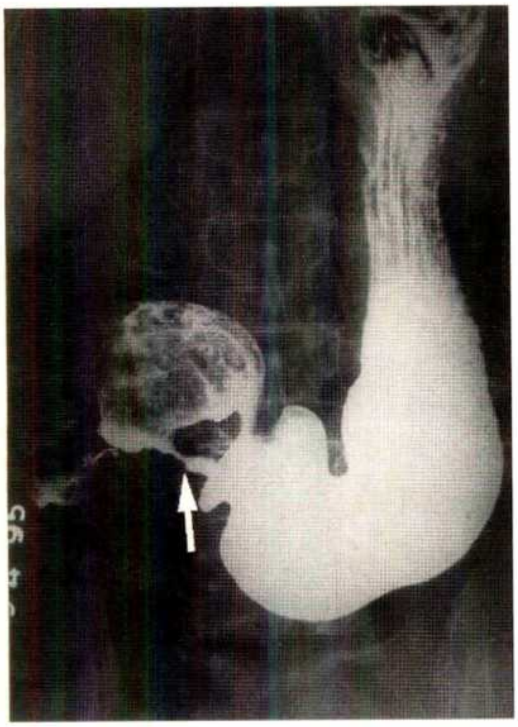

Fig. 1 Barium meal showing an intraluminal mass in the gastric antrum and first part of duodenum. Leakage of contrast from the duodenum is seen (arrow). At operation the mass was found to be necrotic pancreas and peripancreatic tissue which had eroded into the lumen

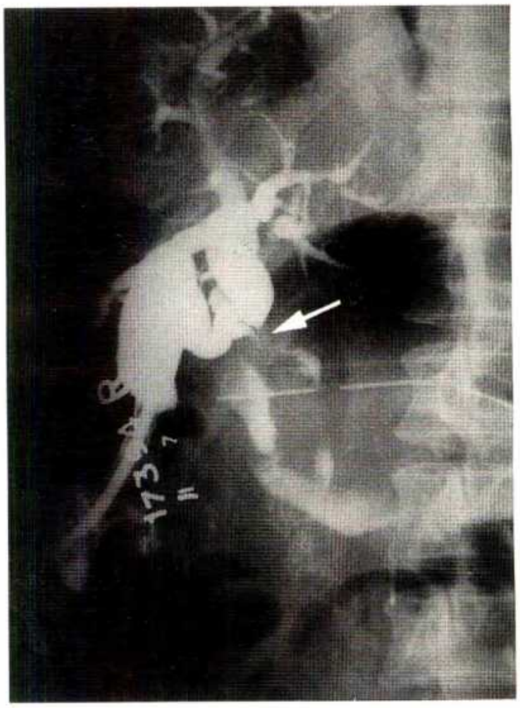

Fig. 2 Cholecystocholangiogram in a patient with erosion of the bile duct demonstrating narrowing in the bile duct (arrow) with proximal dilatation

Table 1 Clinical details of 17 patients with locoregional complications of pancreatic necrosis

Organ involved	Complications	Presentation	Operative procedures*	Deaths
Stomach	Perforation (3)	Haematemesis (1)	Closure	2
Duodenum	Medial wall erosion (2)	Haematemesis	Suture ligation of bleeding vessel (1) Pancreaticoduodenectomy (1)	2
	Lateral wall erosion (3)	Pneumoperitoneum (1)	Serosal onlay patch (2) Closure (1)	–
	Anteroinferior wall erosion (1)	Gastric outlet obstruction	Serosal onlay patch	–
Jejunum	Gangrene (1)	Peritonitis	Resection and anastomosis	–
	Perforation (1)	Pneumoperitoneum	Resection and anastomosis	–
Colon	Necrosis (1)	Melaena	Transverse colectomy, colostomy, mucous fistula	1
	Perforation (2)	Peritonitis (1)	Closure with colostomy	1
Biliary tract	Gallbladder perforation (1)	Biliary peritonitis/Jaundice	Partial cholecystectomy	–
	Bile duct erosion (1)	Biliary peritonitis	Cholecystostomy	–
Spleen	Splenic erosion (1)	Haemoperitoneum	Splenectomy	–

Values in parentheses are number of patients. *In addition to pancreatic necrosectomy sepsis. One patient developed a gastrocutaneous fistula after closure of a gastric perforation, and one had a duodenal fistula following suture closure of a duodenal perforation. Both patients were managed conservatively. Hospital stays of these patients ranged from 2 to 78 (mean 59) days.

Six of the 17 patients with locoregional complications died in hospital, 2–54 days after admission, the cause of death being multiorgan dysfunction. The mortality rate was higher in patients with gastric and colonic involvement. Of the 66 patients without locoregional complications, ten patients (15 per cent) died.

At follow-up two patients had developed incisional hernias. In the patient with erosion of the bile duct, cholecystocholangiography done 6 weeks after surgery showed narrowing of the distal bile duct with proximal dilatation (*Fig. 2*) and cholecystectomy with Roux-en-Y choledochojejunostomy was done to relieve biliary obstruction.

Discussion

Infected pancreatic necrosis can cause significant damage to peripancreatic viscera. The resulting complications necessitate the addition of another procedure to pancreatic necrosectomy making it a formidable exercise. The presence of acute inflammation associated with pancreatic necrosis and the co-existing infection enhances the chances of disruption of suture lines and increases the postoperative mortality and morbidity rates. Such locoregional complications caused directly by pancreatic necrosis have rarely been discussed. In two recent articles, only 7 per cent of patients were recognized to have gastrointestinal fistulas at the initial operation[6,7]. The present review is one of the largest reported experiences of the number and type of complications caused by the necrotic process associated with acute pancreatitis. The high incidence of complications (17 of 83 patients; 20 per cent) seen in these patients is probably due to the delayed referral, since the longer the infective process is allowed to persist, the higher are the chances of damage to the peripancreatic structures. The mean interval between the onset of pancreatitis and the time of intervention was 46 days, in contrast to 29 days for patients in whom no complication was detected during surgery. Although pancreatitis associated with gallstones is regarded to be more severe than alcoholic pancreatitis the incidence of complications was found to be similar in both groups. The cause of involvement of peripancreatic structures in pancreatic necrosis is multifactorial. Extravasated pancreatic secretions most often directly damage an organ by their enzymatic nature or may produce vascular thrombosis leading to ischaemic injury. Early in the course of acute pancreatitis, hypovolaemic shock with a splanchnic low flow state may occur because of inadequate fluid replacement and this may contribute to the overall ischaemic insult[6,7]. The presence of shock, gastrointestinal bleeding, peritonitis, jaundice and pneumoperitoneum in a patient with pancreatic necrosis are indicators of an associated complication. The presence of OSF at the time of admission was observed to be more common in patients with complications of the necrotic process indicating the seriousness of the condition. The presence of complications has considerable clinical implications as these patients may need urgent surgical intervention to limit the ongoing sepsis.

Perforations of the stomach because of pancreatic necrosis were found to occur on the posterior wall of the stomach; such perforations present either with haematemesis or may be detected only at surgery. Although technically easy to close, the chances of breakdown of these closures are high as the suture line lies in the vicinity of the infected pancreas and its digestive ferments. The resulting gastrocutaneous fistula is a serious problem with a high associated mortality rate mainly because of the risk of bleeding. Warshaw *et al.*[8] recommend early surgery to close these fistulas because of their aggressive behaviour. Interposition of omentum between the stomach and the pancreas may be a useful adjunct to avoid breakdown of the suture line.

Erosion of the medial wall of the duodenum in patients with pancreatic necrosis is one of the most difficult complications to manage. Both patients with such lesions in this study presented with haematemesis and died after operation. Pancreaticoduodenectomy, although an ideal operation for such lesions, is a formidable proposition in these sick patients. In contrast, perforations of the lateral aspect of duodenum are easier to manage; a serosal onlay patch using a jejunal loop gives good results. Local closure usually fails because of the inflamed and oedematous edges of the perforation[9]. In such perforations, duodenal decompression using a tube passed in a retrograde fashion has been recommended as an additional safety measure[10]. As oral intake is withheld in these patients, tube jejunostomy for enteral feeding is a useful adjunct. Contrary to some reports[11] no problems were encountered in the institution and maintenance of feeding through the jejunostomy. Small bowel involvement in pancreatic necrosis may be either as a perforation or gangrene due to thrombosis of vessels in the mesentery[5]. These patients may present with prolonged ileus, gastrointestinal bleeding, peritonitis or evidence of pneumoperitoneum along with features of severe acute pancreatitis. Resection of the involved area is the safest option.

Involvement of the colon is a well recognized complication of acute pancreatitis and it is estimated that about 2 per cent of patients develop colonic complications in the course of the illness[12,13]. The colonic complications in acute pancreatitis include ileus, fistula formation, perforation and colonic necrosis[14–17]; the usual sites of involvement of the colon are the transverse colon and the splenic flexure, because of their proximity to the pancreas, and the poor collateral flow. In the authors' experience, all three patients with colonic involvement had necrosis extending on to the transverse mesocolon suggesting an ischaemic basis for the lesions. Patients with colonic fistulas tend to do worse than those with other fistulas, and the mortality rate may exceed 50 per cent[18]. The accepted treatment of colonic complications of acute pancreatitis is resection of the non-viable colon and proximal colostomy. Diverting loop ileostomy at the time of pancreatic necrosectomy has been advocated[16], when colonic ischaemia is either present or expected to become a problem. An elective colostomy closure should be done 6 months or more after the initial surgery to allow the inflammation and oedema associated with pancreatitis to subside.

Splenic lesions in acute pancreatitis include haematomas, infarction, rupture, erosion of the splenic artery or thrombosis of the splenic vein[19–22]. Pancreatic secretions can dissect into the splenic hilum as the splenic capsule is continuous with the peritoneum covering the anterior surface of the pancreas. These patients usually present with intra-abdominal haemorrhage and splenectomy may be required[21]. Although Donckier *et al.*[22] reported a case of subcapsular splenic laceration that was managed conservatively, attempts at conservation of the spleen in the presence of active sepsis can be dangerous.

Perforation of the gallbladder or the bile duct is extremely rare in pancreatic necrosis. Both patients with this complication had biliary peritonitis. Schein *et al.*[23] reported a case of gallbladder necrosis due to erosion by the infected pancreatic necrosis. Like the present patient, their patient also underwent a partial cholecystectomy; the bleeding edges confirmed the patency of the cystic artery and ruled out acalculous cholecystitis. In the other patient in the present study with biliary peritonitis, the extensive necrosis had eroded the infracystic part of the bile duct, as the remaining duct was thin walled and collapsed; a cholecystostomy was done. Subsequently the distal duct strictured and needed a hepaticojejunostomy, thereby suggesting that acute pancreatitis can also cause strictures in the bile duct. Miller *et al.*[24] reported a somewhat similar case wherein the pancreatic necrosis had eroded the lower end of the bile duct and adjacent pancreatic duct remnant, necessitating pancreaticoduodenectomy.

Necrosis associated with acute pancreatitis can cause widespread damage to various organs in the vicinity of the pancreas. Awareness of the existence of such complications can prevent delay in surgical intervention, a factor which adversely affects the outcome. Although these locoregional complications are associated with an increased mortality rate, timely intervention before development of OSF and a well planned management protocol may improve survival.

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Hepatolithiasis associated with cholangiocarcinoma

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Background Intrahepatic stone is common in East Asia. Hepatolithiasis is a risk factor for cholangiocarcinoma but it is difficult to make an accurate diagnosis before operation. The effect of intrahepatic stone on diagnosis, treatment and survival in patients with coexistent cholangiocarcinoma was investigated.

Methods Between 1981 and 1994, 33 patients with hepatolithiasis and associated cholangiocarcinoma were identified and compared respectively to 18 patients with intrahepatic cholangiocarcinoma alone.

Results Patients with intrahepatic stones had a significantly longer duration of symptoms, a higher frequency of previous biliary surgery but a lower rate of preoperative diagnosis. Surgical resection was the treatment of choice and was performed in 18 of 33 patients with cholangiocarcinoma and stones and in nine of 18 with intrahepatic cholangiocarcinoma alone. Significantly inferior 5-year survival rates were found in patients with hepatolithiasis: two of 32 *versus* four of 14 for all cases and two of 17 *versus* four of nine for resectable cases ($P < 0{\cdot}05$).

Conclusion These survival differences may be attributed to delayed diagnosis, lower diagnostic rate and relatively fewer curative resections in the patients with stone-containing cholangiocarcinoma.

Intrahepatic stone is uncommon in Western countries but prevalent in East Asia. Taiwan has long been noticed to have the highest prevalence among the Asian countries[1,2]. Recently, a nationwide cooperative study was conducted in Taiwan and the prevalence of intrahepatic stone over the past 20 years in the whole country was found to be about 20 per cent[3]. The association of hepatolithiasis with cholangiocarcinoma has been thought rare, previously reported to be 4–11 per cent[4–11]. Despite the improvement of imaging studies in recent years, accurate preoperative diagnosis remains low[5,10–12] and the survival outcome is still dismal[11,12].

The purpose of this study was to review cases and re-evaluate the effect of hepatolithiasis on the diagnosis, treatment and survival of patients with coexistent cholangiocarcinoma.

Patients and methods

Between 1981 and 1994, 816 patients with hepatolithiasis were treated surgically at this hospital. Of these, 33 patients were found to have associated cholangiocarcinoma, including 27 with intrahepatic cholangiocarcinoma (ICC) and six with hilar cholangiocarcinoma (Klatskin tumour). In the same period, a further 18 cases of ICC without coexistent intrahepatic stones were also reviewed for comparison. Of these 18 patients, nine had pure peripheral-type cholangiocarcinoma and nine had the main tumour in the liver parenchyma and infiltrating the hepatic hilum to cause obstructive jaundice.

The clinical presentation and diagnostic investigations including ultrasonography, computed tomography (CT) and cholangiography were carefully reviewed. The operative findings, operative procedure and survival outcomes were recorded.

Statistical analysis was performed with Student's t test for the differences between means. Values are presented as mean(s.d.). Differences in proportions were determined by Fisher's exact test. The Kaplan–Meier method was used to calculate the probability of overall survival and the generalized Wilcoxon test to evaluate the significance of survival in each subset of patients. $P < 0{\cdot}05$ was considered statistically significant.

Results

The sex and age distribution of the two groups was similar. Patients with cholangiocarcinoma and intrahepatic stones had a longer duration of symptoms and more frequent biliary operations than those with ICC alone (*Table 1*). Right upper quadrant pain, fever, chills and jaundice were the most frequent symptoms encountered in the group with cholangiocarcinoma and intrahepatic

Table 1 Clinical details of patients with cholangiocarcinoma and hepatolithiasis

	CC with IHS ($n = 33$)	ICC ($n = 18$)
Sex ratio (M:F)	18:15	13:5
Mean(s.d.) age (years)	60(9)	62(10)
Mean(s.d.) duration of symptoms (years)	7·9(10·6)	0·3(0·4)*
Previous biliary surgery	17	1†
Symptoms		
Right upper quadrant pain	30	11
Fever and chills	20	2
Jaundice	11	9
Loss of body-weight	8	3
Abdominal mass	4	3
Pruritus	2	3
General malaise	3	2
Ascites	0	1

CC, cholangiocarcinoma; IHS, intrahepatic stone; ICC, intrahepatic cholangiocarcinoma. *$P < 0{\cdot}005$ *versus* CC with IHS (Student's t test); †$P < 0{\cdot}005$ *versus* CC with IHS (Fisher's exact test)

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stones, whereas pain and jaundice were the predominant symptoms in patients with ICC alone (*Table 1*).

The incidence of cholangiocarcinoma in patients with intrahepatic stones in this series was 4 per cent (33 of 816). The location of stones and cholangiocarcinoma in these 33 patients is tabulated in *Table 2*. After exclusion of six patients in whom the tumour was located mainly at the hepatic hilum, the tumour and stones were closely related in 26 of 27 patients with ICC and hepatolithiasis, being located differently in only one patient.

Various imaging studies including ultrasonography, CT, cholangiography and angiography were performed for diagnosis (*Table 3*). Only 14 of the 33 patients with cholangiocarcinoma and intrahepatic stones were found to have a correct diagnosis before operation, however. If the hilar tumours were excluded, the accurate diagnostic rate for patients with ICC and intrahepatic stones was only nine of 27. In contrast, a statistically significant higher diagnostic rate (13 of 18 patients) was observed in the ICC group ($P < 0{\cdot}05$).

A radiological finding of segmental stricture and dilated intrahepatic ducts was the most common observation in patients with or without coexisting intrahepatic stones (*Table 4*). Tumour mass observed on the imaging study was encountered frequently in the ICC group (13 of 15 patients), which would in turn increase its diagnostic rate. A coexisting tumour with atrophic liver in patients with hepatolithiasis should arouse the suspicion of coexistent cholangiocarcinoma. Careful choledochoscopy performed either during or after operation was diagnostic in three of six patients (*Table 4*). In suspected lesions, preoperative fine-needle aspiration biopsy is a good adjunct to obtain a positive diagnosis (*Table 4*).

So far, no specific tumour markers are available for diagnosis of cholangiocarcinoma. However, raised levels of carcinoembryonic antigen (CEA) and/or CA19-9 were frequently encountered: abnormal CEA concentration was present in 11 of 16 patients with cholangiocarcinoma and intrahepatic stones and in nine of 16 in the ICC group, and CA 19-9 level was increased in seven of nine and three of eight patients respectively. Mean(s.d.) CEA levels in patients with resected and unresected cholangiocarcinoma were 39·0(20·6) and 166·9(96·1) ng/ml (cholangiocarcinoma and intrahepatic stones), and 26·1(7·2) and 96·3(43·7) ng/ml (ICC group) respectively. The mean(s.d.) CA19-9 concentration in the resected and unresected groups was 1107(520) and 18 460(12 640) units/ml (cholangiocarcinoma and intrahepatic stones) and 72(44) and 7677(10 764) units/ml in patients with ICC alone. Although higher levels of tumour markers were noticed in the irresectable groups, the differences were not statistically significant. A raised level of CEA and/or CA19-9 does not always indicate incurability. Seven of 20 patients with increased CEA levels and five of ten with increased CA19-9 levels had a resectable lesion.

Although cholangiocarcinoma is a relatively slow-growing tumour, nearly half of the patients in this series were beyond surgical resection. Only 18 patients with cholangiocarcinoma and intrahepatic stones and nine in the ICC group had resectable tumour. Liver resection of variable extent was the main surgical treatment (*Table 5*). Potentially curative resection, as evaluated by a clear resection margin, was achieved in five of nine patients with ICC, in four of 13 with cholangiocarcinoma alone, and in three of 12 with ICC and intrahepatic stones. One patient with cholangiocarcinoma and intrahepatic stones died from hepatic failure after operation and four with

Table 2 Location of intrahepatic stones and cholangiocarcinoma in 33 patients

Intrahepatic stones	Cholangiocarcinoma				
	Right	Left	Both	Hilum	Total
Right	6	1	0	1	8
Left	0	12	1	3	16
Both	4	2	1	2	9
Total	10	15	2	6	33

Table 3 Diagnostic accuracy of imaging studies in cholangiocarcinoma

	CC with IHS	ICC
Ultrasonography	11 of 33	12 of 16
Computed tomography	13 of 22	12 of 12
Percutaneous transhepatic cholangiography	7 of 13	6 of 6
Endoscopic retrograde cholangiopancreatography	8 of 17	5 of 6
Angiography	1 of 2	7 of 8
Magnetic resonance imaging	1 of 1	2 of 2

CC, cholangiocarcinoma; IHS, intrahepatic stone; ICC, intrahepatic cholangiocarcinoma

Table 4 Possible clues to the diagnosis of cholangiocarcinoma

	CC with IHS	ICC
Stricture or stenosis on cholangiogram	23 of 28	9 of 12
Dilatation of intrahepatic duct	31 of 33	8 of 12
Tumour mass	16 of 33	13 of 15
Liver atrophy	11 of 33	1 of 12
Positive choledochoscopy	3 of 6	0 of 2
Positive fine-needle aspiration biopsy	6 of 6	4 of 4

CC, cholangiocarcinoma; IHS, intrahepatic stone; ICC, intrahepatic cholangiocarcinoma

Table 5 Management of patients with cholangiocarcinoma

	CC with IHS ($n = 33$)	ICC ($n = 18$)
No operation	3	3 (1)
Exploratory laparotomy biopsy with or without T tube	12	6 (3)
Right lobectomy	6	2
With caudate lobectomy	2	0
With CBD resection	1	0
With caudate lobe and CBD resection	1	0
Right trisegmentectomy with caudate lobe and CBD resection	0	1
Left lobectomy	6	5
With CBD resection	2	2
With caudate lobe and CBD resection	2 (1)	2
Segmentectomy	4	1
CBD resection only	2	0

Values in parentheses are deaths in hospital. CBD, common bile duct; CC, cholangiocarcinoma; IHS, intrahepatic stone; ICC, intrahepatic cholangiocarcinoma unresected ICC died from cachexia and sepsis during hospitalization.

All patients were followed periodically until death. Patients with resectable lesions clearly had longer survival than those with an irresectable lesion (*Fig. 1*). Survival was better in patients with ICC alone than in those with stones and cholangiocarcinoma ($P<0{\cdot}05$) (*Fig. 2*). Among the resected cases, the 5-year survival rate was 42 per cent in the ICC group, which was significantly better than 6 per cent in those with cholangiocarcinoma and intrahepatic stones (*Fig. 1*). When the five patients with hilar tumours were excluded from the latter group, no patient with ICC and stones survived more than 3 years (*Fig. 3*).

Discussion

Cholangiocarcinoma has been reported in association with polycystic liver disease[13], *Clonorchis sinensis* infection[14,15] and choledochal cyst[16]. In 1942, Sanes and MacCallum[17] first reported two cases of primary carcinoma of the liver complicating hepatolithiasis. Later, several case reports were added[4–11,18,19] and the largest series was reported recently by Chen *et al*[11]. The incidence of coexistent cholangiocarcinoma in patients with intrahepatic stones has been reported to be 1·5–9·4 per cent in Japan[6] and as 2·4–5·0 per cent in Taiwan[5,8,10,11,20]. It was 4 per cent in the present series.

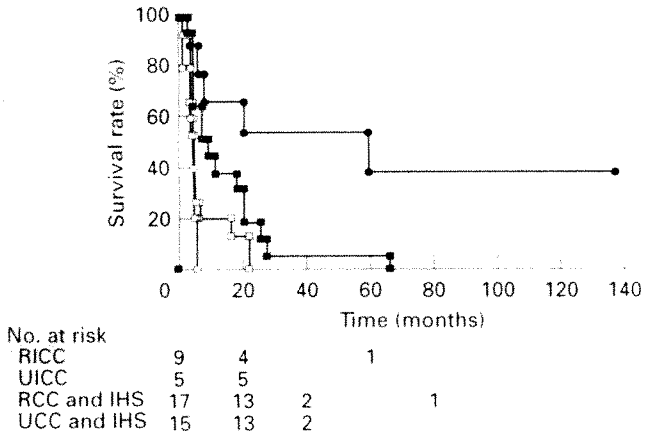

Fig. 1 Cumulative survival rate of patients with resectable and irresectable cholangiocarcinoma with or without coexistent hepatolithiasis. ○, Unresected intrahepatic cholangiocarcinoma (ICC) without coexistent intrahepatic stones (IHS); ●, resected ICC; □, unresected cholangiocarcinoma (CC) with IHS; ■, resected CC with IHS. $P<0{\cdot}05$ (resected ICC *versus* unresected ICC and resected CC with IHS; resected *versus* unresected CC with IHS, Wilcoxon test)

The pathogenesis of intrahepatic stones with cholangiocarcinoma is not completely understood. In the opinion of most authors, chronic bacterial infection, bile stasis and mechanical irritation of hepatolithiasis can lead to the development of mucosal adenomatous hyperplasia and chronic proliferative cholangitis[4,21–24]. Chronic proliferative cholangitis in the presence of hepatolithiasis can undergo progressive change to atypical epithelial hyperplasia, which may in turn progress to cholangiocarcinoma[4,21]. However, the stone itself does not provide the sole carcinogenic stimulus leading to malignancy. One of the present patients had cancer in the left lobe but hepatolithiasis occurred only in the right lobe, and another patient had tumours in both lobes of the liver but stones in the left lobe only (*Table 2*). It is probably the cumulative results of several aetiological factors, such as nutritional, genetic, environmental and immunological abnormalities, that are responsible for its carcinogenesis.

Accurate preoperative diagnosis is usually difficult. The diagnostic rate has been reported to range from 0 to 37·5 per cent[5,10–12]. In most patients the diagnosis was made during the operation. This was also true in the present series, despite various imaging studies. Accurate preoperative diagnosis was made in only 14 of 33 patients with cholangiocarcinoma and intrahepatic stones and in nine of 27 with ICC and stones.

Three reasons may be implicated for this lower diagnostic rate in patients with cholangiocarcinoma and intrahepatic stones. First, hyperechoic stone shadows in the sonogram usually mask the coexisting tumours and dilated intrahepatic ducts. Second, a space-occupying lesion in the liver may make it difficult to differentiate between abscess and malignancy (*Fig. 4*). Third, the infiltrative tumour usually causes a strictured segment, which hinders detailed examination of the distal intrahepatic duct on cholangiography or choledochoscopy.

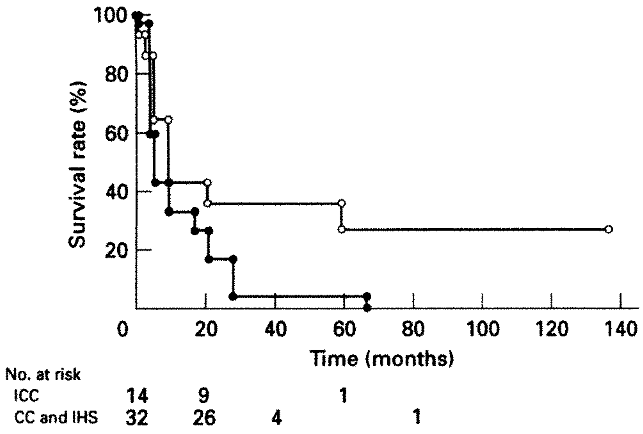

Fig. 2 Cumulative survival rate of all patients with cholangiocarcinoma. ○, Intrahepatic cholangiocarcinoma (ICC) without coexistent intrahepatic stones (IHS); ●, cholangiocarcinoma (CC) with IHS. $P<0{\cdot}05$ (Kaplan–Meier)

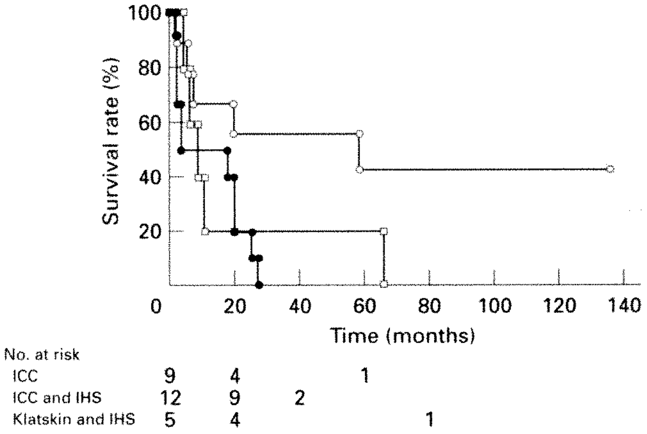

Fig. 3 Cumulative survival rate of patients with resectable cholangiocarcinoma. ○, Intrahepatic cholangiocarcinoma (ICC) without coexistent intrahepatic stones (IHS); ●, ICC with IHS; □, Klatskin tumour with IHS. $P<0{\cdot}05$(ICC *versus* ICC with IHS); Wilcoxon test)

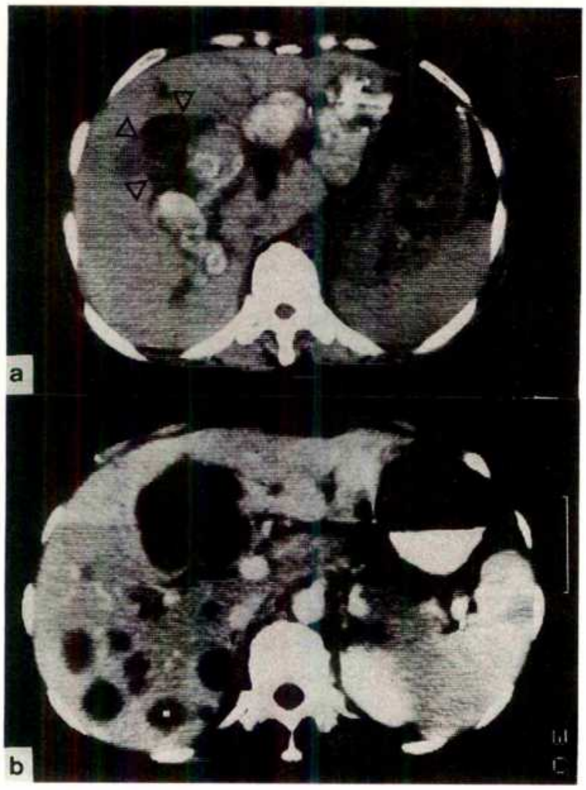

Fig. 4 A 44-year-old woman presented with cholangitis. **a** Computed tomography (CT) revealed multiple intrahepatic stones with a suspected liver abscess (arrow heads). Choledocholithotomy was performed and the stones were completely removed after six sessions of postoperative choledochoscopy. **b** Unfortunately, epigastric pain persisted and follow-up CT 2 months later disclosed multiple metastatic lesions involving both lobes of the liver

Choledochoscopy is a routine adjunctive procedure in the treatment of hepatolithiasis. The finding of intramural tumour or so-called mucobilia[11] is a crucial feature in suspecting a coexistent tumour, whether it is a central or peripheral type of cholangiocarcinoma. Although all 33 patients with stone-containing tumours in this series had postoperative choledochoscopy, this was usually carried out in the previous biliary surgery. In only six patients was choledochoscopy performed in the presence of tumour immediately after operation. Unfortunately, three of these had misdiagnoses. Two patients had tumour dissemination 2 and 6 months after the stones had been removed completely (*Fig. 4*). One patient had a palliative right lobectomy 3 months after the last choledocholithotomy and choledochoscopy. Multiple liver metastases were noticed grossly and tumour emboli in the portal veins were the predominant microscopic findings. It seems that repeated trauma during choledochoscopic stone removal in a misdiagnosed patient will result in frequent tumour emboli in the portal veins, which will in turn facilitate tumour dissemination and preclude a curative resection.

To improve the accuracy of diagnosis, a high index of suspicion is mandatory in the management of hepatolithiasis. A strictured intrahepatic duct, the presence of a liver mass in association with a dilated peripheral biliary tree, a coexisting tumour in an atrophic liver and raised CEA or CA19-9 level should arouse the suspicion of coexistent cholangiocarcinoma. Furthermore, careful choledochoscopic examination to identify intramural lesions or mucobilia[11], and repeated choledochoscopic biopsy or fine-needle aspiration biopsy of the suspected lesions, are strongly advocated to obtain a positive diagnosis.

The prognosis of patients with hepatolithiasis with associated cholangiocarcinoma is poor[11,12]. Despite hepatic resection in suitable cases, the 5-year survival rate in this series was only 3 per cent consistent with the 4-year survival rate of 4 per cent reported by Chen *et al*[11]. Until now, there has been no report on the effect of intrahepatic stones on the survival of patients with coexistent cholangiocarcinoma.

It was interesting to find in this study that cholangiocarcinoma with stones was associated with a significantly poorer survival than cholangiocarcinoma alone (*Figs. 1–3*). Several factors may explain such a difference. First, the mean duration of symptoms was significantly longer in the patients with stones. A delayed diagnosis secondary to a longer duration of symptoms may be the underlying cause of the poor prognosis. Actually it is hard to identify the time span required for the bile duct to undergo malignant change because of the long period of time. Second, the lower preoperative diagnostic rate in patients with cholangiocarcinoma and intrahepatic stones delayed early detection and treatment of the cholangiocarcinoma. Third, potentially curative resection, as evaluated by a clearly resected margin, was possible in more of the patients with ICC (five of nine) than of those with cholangiocarcinoma and intrahepatic stones (four of 13) or with ICC and stones (three of 12). Finally, the adverse effect of postoperative choledochoscopy in a misdiagnosed patient will result in delayed diagnosis and tumour dissemination, and may preclude radical resection.

In conclusion, intrahepatic stone disease is uncommon in the Western world but is prevalent in the East Asian countries. The potentially malignant change in 4–5 per cent of these cases should be kept in mind in the management of hepatolithiasis. Every effort should be made to reach an early diagnosis. Surgical resection appears to be the only way to improve long-term survival.

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Initial experience with an absorbable laparoscopic ligation clip

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Background Laparoscopic surgery requires secure and safe methods of ligation and haemostasis. This study evaluated the efficacy of an absorbable ligation clip with a novel compression closure mechanism.

Methods A new compression-closure absorbable clip was compared with currently available absorbable and non-absorbable clips used in a variety of laparoscopic procedures in 12 centres worldwide.

Results At follow-up to 3 months after the procedure, no complications specific to the use of the compression-closure clip were detected. Operator satisfaction with the clip was high, with criticism directed at its relatively large size.

Conclusion This new clip is as safe and effective as presently available metal and absorbable clips in providing haemostasis and securing tubular structures.

The technique of laparoscopic surgery requires adequate methods for securing haemostasis and closure of tubular structures such as the cystic duct stump during cholecystectomy. The currently available metal ligation clips, while satisfactory in the majority of cases, suffer certain drawbacks. These include electrical current conduction, ease of dislodgement, interference with imaging techniques such as computed tomography and magnetic resonance imaging, and acting as a nidus for common bile duct stone formation[1–4]. The currently available absorbable clips rely on a latch mechanism, which may be impeded if tissue becomes interposed between the jaws, causing incomplete closure[5,6].

This study was designed to evaluate the performance of a new absorbable ligation clip, with a novel compression closure mechanism, for use in laparoscopic surgery in comparison with metal and currently available absorbable ligation clips.

Patients and methods

The Lapro-Clip (Davis and Geck, Danbury, Connecticut, USA), which is made from a bioabsorbable polymer, is radiolucent and has a novel two-part compression closure mechanism (*Figs 1* and *2*). The inner flexible polyglyconate track piece closes around the vessel or duct, and a rigid outer polyglycolic body then slides over the track piece to occlude the vessel or duct. This closure mechanism reduces the risk of excess tissue interposition causing clip failure. The clip degrades by hydrolysis in 180 days. It is applied with a reusable applicator introduced through a 10-mm port.

A total of 415 patients were entered into the study. In the test group 230 underwent laparoscopic cholecystectomy using Lapro-Clips, and these were compared with 146 unselected prospective

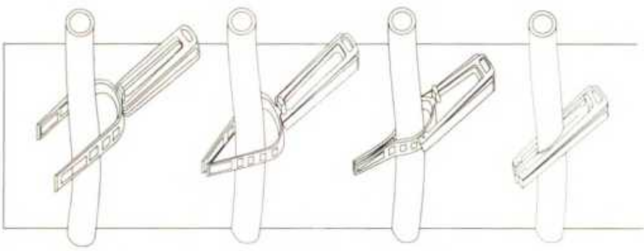

Fig. 1 Closure sequence of the Lapro-Clip

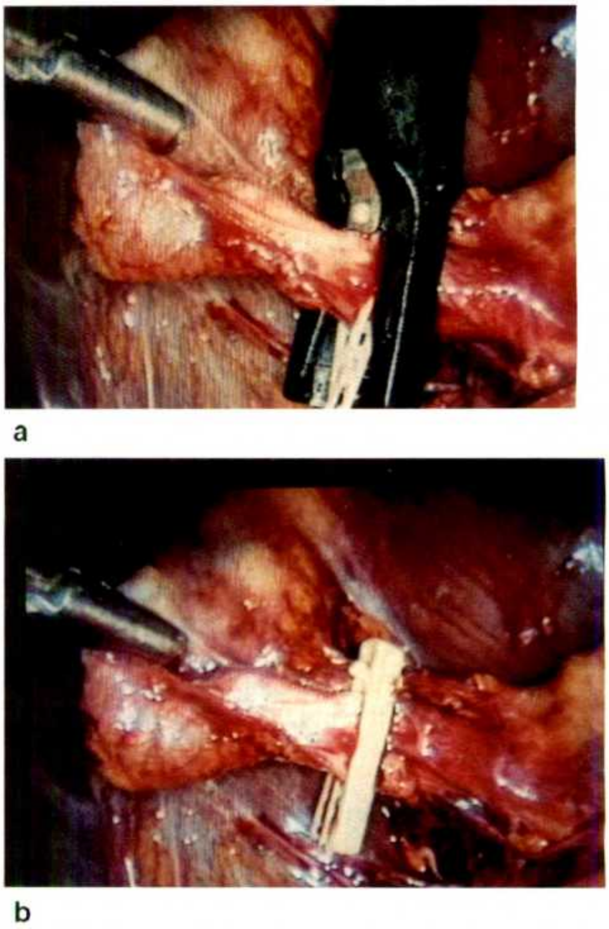

Fig. 2 a Application of the Lapro-Clip to the cystic duct; **b** the Lapro-Clip in place

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control patients having laparoscopic cholecystectomy with metal or latch-closure (Absolok; Ethicon, Somerville, New Jersey, USA) absorbable clips. Twenty-one patients had laparoscopic procedures other than cholecystectomy using the Lapro-Clip; these were matched against 18 controls undergoing laparoscopic procedures other than cholecystectomy with metal or latch-closure (Absolok) absorbable clips (*Table 1*). Forty (24·4 per cent) of 164 control patients had laparoscopic procedures performed with absorbable latch-closure (Absolok) ligation clips. Metal clips applied with either single- or multi-fire applicators were used in the remaining 124 control patients (75·6 per cent).

Patients were enrolled from 12 surgical centres worldwide. The disparity in group size occurred because two centres worked only with Lapro-Clips and provided only historical control data, which were not included in the trial.

Assessments were made of: (1) intraoperative complications; (2) postoperative complications during hospitalization; and (3) postoperative outcome at 1 and 3 months. An unsatisfactory result was recorded when the patient complained of any of the following: persistence of preoperative symptoms, persistent postoperative pain or other postoperative complication such as deep venous thrombosis or wound infection.

Table 1 Operations other than laparoscopic cholecystectomy included in the study

Procedure	Lapro-Clip	Control clip
Adrenalectomy	1	0
Anterior resection	1	1
Appendicectomy	1	4
Colectomy (total or partial)	4	4
Oesophagectomy	1	0
Herniorrhaphy	1	1
Hysterectomy	1	2
Liver biopsy	1	0
Nissen fundoplication	5	3
Oöphorectomy	0	1
Polypectomy	1	1
Sigmoid colectomy	2	0
Thoracoscopic lung resection	1	1
Vagotomy and seromyotomy	1	0
Total	21	18

Table 2 Characteristics of the study subjects

	Lapro-Clip group ($n = 251$)	Control group ($n = 164$)
Mean(s.d.) (range) age (years)	50·7(15·3) (14–90)	50·5(15·6) (18–83)
Sex ratio (M:F)	82:169	49:115
Mean(s.d.) weight (kg)	73·0(14·6)	74·6(26·3)

The surgeons involved were also asked to assess the handling characteristics and subjective security of the Lapro-Clip in comparison with controls for each case by completion of a standardized questionnaire.

Results

The demographic features of the groups were similar (*Table 2*).

The only clip-related complication was one minor bleeding episode during operation due to partial cystic artery occlusion by the Lapro-Clip; this was readily controlled by further clip application. There were no postoperative complications, such as bile leakage or bleeding, related to clip application or use in either group. Total postoperative complication rates were similar for both groups (Lapro-Clip 17 (6·7 per cent) *versus* control nine (5·5 per cent)).

One month after operation 233 patients (92·9 per cent) in the test group were reviewed and two (0·8 per cent) had an unsatisfactory result; in the control group 150 patients (91·5 per cent) were seen and two (1·2 per cent) had unsatisfactory results. These findings were the same at the 3-month review. None of the persisting unsatisfactory results could be attributed to clip-related complications.

There was a high degree of operator satisfaction with the Lapro-Clip loading mechanism, security and clip closure (*Table 3*). However, one criticism was the large size of the Lapro-Clip, which sometimes made full visualization of the distal ends of the clip difficult. The larger size of the clip was advantageous when a large or bulky cystic duct was encountered. A greater proportion of satisfactory results was recorded by assessors in favour of the Lapro-Clip over controls in the areas of clip loading, security and haemostatic effect.

The mean(s.d.) number of Lapro-Clips used was 6·6(1·5) (range 1–30) per patient compared with 7·7(1·8) (range 2–30) control clips per procedure.

Discussion

The results of this study suggest that the Lapro-Clip is as safe and effective as standard metal clips for vessel and

Table 3 Handling characteristics reported by surgeons in 415 cases*

	Lapro-Clip ($n = 251$)		Control ($n = 164$)	
Characteristic	Satisfactory	Unsatisfactory	Satisfactory	Unsatisfactory
Visibility of ligation site	176 (70·1)	70 (27·9)	148 (90·2)	3 (1·8)
Clip size	203 (80·9)	43 (17·1)	149 (90·9)	2 (1·2)
Clip closure	241 (96·0)	6 (2·4)	151 (92·1)	0 (0)
Clip security	241 (96·0)	6 (2·4)	148 (90·2)	3 (1·8)
Clip loading	247 (98·4)	0 (0)	151 (92·1)	0 (0)
Trigger pressure	185 (73·7)	62 (24·7)	151 (92·1)	0 (0)
Visibility of clip	197 (78·5)	50 (19·9)	150 (91·5)	1 (0·6)
Applicator function	223 (88·8)	24 (9·6)	149 (90·9)	2 (1·2)
Haemostasis	241 (96·0)	1 (0·4)	143 (87·2)	0 (0)

Values in parentheses are percentages. *Some assessors failed to provide data for all categories in all cases duct ligation. Its use was not associated with any increase in local or general complications up to 3 months after operation, when compared with metal or currently available latch-closure absorbable clips.

Animal work has suggested that the design of absorbable clips may make them more secure than metal clips that close by simple compression[6]. However, currently available latch-closure clips may fail if tissue becomes interposed between the jaws. The new compression closure mechanism of the Lapro-Clip may provide a more secure closure than latch closure mechanisms by reducing the risk of tissue interposition.

Most of the criticisms of the Lapro-Clip by the operators related to its large size, making visualization of the distal ends of the clip difficult. A smaller 8-mm clip is being developed.

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Long-term survival following resection of colorectal hepatic metastases

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Aim The aim of this study was to analyse characteristics of patients who survived more than 5 years after liver resection of colorectal metastases.

Methods A multicentre retrospective study collected 1818 patients who underwent curative resection of hepatic metastases between 1959 and 1991. Among the 747 patients operated on before 1987, 102 survived longer than 5 years, and were compared with patients who survived less than 5 years.

Results Three risk factors proved independently significant in multivariate analysis between the two groups: serosa infiltration ($P = 0{\cdot}003$), involvement of peritumoral lymph nodes around the primary colorectal tumour ($P = 0{\cdot}04$), and a liver resection margin of less than 1 cm ($P = 0{\cdot}02$). There was no significant difference for other parameters studied (location of primary tumour, location, number and size of metastases, type of resection). A trend towards a shorter survival of patients with increased carcinoembryonic antigen serum level was observed.

Conclusion Resection of colorectal hepatic metastases can provide long-term survival even in patients with poor prognostic factors. It seems justified to undertake resection of colorectal liver metastases whenever it may be performed safely as a curative treatment.

Surgical resection is widely accepted as the only potentially curative treatment for patients with colorectal liver metastases[1,2]; it is also the only treatment that can offer long-term survival[1,3–6]. After resection, the mean 5-year survival rate is close to 25 (range 16–45) per cent[1–6]. These results were confirmed in a large multicentre retrospective study undertaken by the Association Française de Chirurgie (AFC)[7], which analysed the largest presently available series of liver resections for metastasis. It confirmed that several factors were of significant predictive value concerning the length of survival. These factors were: local extension of primary colorectal tumour, delay between primary tumour and resection of metastases, number and size of liver metastases, and preoperative carcinoembryonic antigen (CEA) level. In addition, it showed that radicality of liver resection appeared to be the most important prognostic factor: when resection was considered incomplete, there were no 5-year survivors. However, it has been shown in several series that, even among patients who undergo liver resection with curative intent, only a small proportion survive for more than 5 years[2,8,9]. The aim of the present study was to report and analyse the characteristics of long-term survivors and to compare them with patients who survived less than 5 years (short-term survivors).

Patients and methods

Between April and June 1991, a multicentre retrospective study of liver resection for colorectal metastases was undertaken among the members of the AFC. All participating members responded to a questionnaire regarding the primary tumour and liver metastases. This recorded type and date of resection, operative and long-term outcome regarding survival, patient status and, if necessary, treatment of recurrence. Two types of questionnaires were issued: a conventional paper and a computerized backing sheet (FoxPRO; AB Soft, Paris, France). Eighty-five institutions participated in the study. Some 1895 forms containing the required information were returned. In 77 patients the resection was considered incomplete. In this group, overall 5-year survival was nil. In 1818 patients, resection of hepatic metastases was considered to be curative (i.e. macroscopically complete); in this group the overall 5-year survival rate was 26 per cent. In the present study, analysis was focused on the 747 patients who underwent a curative operation between 1959 and 1987. Thus, the last patient included in this interval had at least a 5-year period of follow-up.

Twenty-seven patients died after operation and were excluded; 102 patients survived longer than 5 years (long-term survivors); and 618 survived for less than 5 years (short-term survivors). In the latter group there were 476 patients with complete follow-up data who died before 5 years. For the remaining patients, data were incomplete and it was decided to consider them as short-term survivors, to avoid any overestimation in survival rate. The database was complete and updated for all long-term survivors. Liver resection was performed after 1980 in 83 long-term survivors and 599 short-term survivors.

The groups were compared using the following factors: age, sex, site of primary tumour, serosa or perirectal fat invasion of the primary tumour shown by histological examination of the resected specimen, delay between resection of primary tumour and of hepatic metastases, size and site of metastases as measured on the resected specimen, margin of healthy tissue removed together with the metastasis, type of hepatic resection, CEA level before liver resection, and administration of adjuvant chemotherapy.

The variables were compared with the χ^2 test. Results were expressed as relative risk, and the 95 per cent confidence

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intervals were calculated using Taylor series. A logistic regression model was thereafter applied to identify the independent variables that were significantly related to long-term survival.

Results

Characteristics of long-term survivors

Of the 102 patients who survived more than 5 years, 65 were still alive at the time of the study: 42 (65 per cent) were free of any residual cancer, and 23 showed recurrent metastases. Of these recurrences, 16 were hepatic and eight were pulmonary (one patient had one pulmonary and one hepatic recurrence). Eleven of the 23 patients were treated by resection of the recurrence. Thirty-seven patients died after 5 years. For these patients, death occurred a mean of 75 months after hepatic surgery. The cause of death was obviously the disease in 20 patients.

Comparison between long- and short-term survivors

Age and sex ratio were similar in the two groups: mean 58·7 and 56·9 years and 1·1 and 1·6 respectively for short- and long-term survivors.

Characteristics of the primary tumour are reported in *Table 1*. There was no difference between the two groups regarding the colonic or rectal localization of the tumour. However, in the long-term survivors, tumours were less often infiltrative than in the short-term survivors. Patients without serosa infiltration were twice as likely to survive longer than 5 years, and among patients without peritumoral lymph node invasion the relative risk of long-term survival was 1·6.

Characteristics of liver metastases and their treatment are reported in *Table 2*. Size and number of metastases, liver localization, and delay between treatment of the primary tumour and liver resection had no influence on length of survival. The number of patients in whom liver

Table 1 Relative risk of long-term survival in 720 patients who underwent curative resection of hepatic metastases in relation to primary colorectal tumour characteristics

	No. of long-term survivors ($n = 102$)	No. of short-term survivors ($n = 618$)	Relative risk	P*
Location				
Rectum	34	227	1·0	
Colon	67	385	1·1 (0·8–1·7)	0·51
Astler–Coller stage				
C	44	354	1·0	
A–B	47	187	1·8 (1·2–2·6)	0·002
Serosa infiltration				
Yes	44	387	1·0	
No	58	231	2·0 (1·3–2·8)	<0·001
Peritumoral lymph node invasion				
Yes	44	355	1·0	
No	58	263	1·6 (1·1–2·4)	0·007

Values in parentheses are 95 per cent confidence intervals. *χ^2 test

Table 2 Relative risk of long-term survival in 720 patients who underwent curative resection of hepatic metastases in relation to characteristics of metastases and their treatment

	No. of long-term survivors ($n = 102$)	No. of short-term survivors ($n = 618$)	Relative risk	P*
Carcinoembryonic antigen (ng/ml)				
<5	15	72	1·0	
5–30	21	123	0·8 (0·5–1·6)	0·59
>30	21	227	0·5 (0·3–0·9)	0·02
Location within liver				
Bilobar	10	108	1·0	
Unilobar	90	501	1·8 (1·0–3·4)	0·05
Size of largest metastases (cm)				
>5	45	319	1·0	
<5	55	261	1·4 (1·0–2·0)	0·06
No. of metastases				
>3	7	76	1·0	
1–3	94	525	1·8 (0·9–3·8)	0·13
Delay between resection of primary tumour and hepatic metastases (months)				
>3	58	397	1·0	
≤3	43	219	1·3 (0·9–1·8)	0·17
Type of resection				
Major	63	393	1·0	
Minor	39	225	1·1 (0·7–1·6)	0·73
Tumour clearance				
Edge or < 1 cm	14	148	1·0	
≥ 1 cm	81	388	2·0 (1·2–3·4)	0·008
Adjuvant chemotherapy				
No	62	431	1·0	
Yes	40	187	1·4 (1·0–2·0)	0·07

Values in parentheses are 95 per cent confidence intervals. *χ^2 test metastases were resected more than 3 months after colorectal surgery was similar in both groups (64 *versus* 57 per cent). High CEA level (greater than 30 ng/ml) at time of liver resection was associated with shorter survival, but the CEA concentration before resection was available for only half of the long-term survivors.

As shown in *Table 2*, the type of hepatic resection had no influence on survival. However, the margin of tumour-free parenchyma removed with the metastasis was of important prognostic value, and patients with a resection margin greater than 1 cm were twice as likely to survive more than 5 years. Indeed, only 15 per cent of long-term survivors had a resection margin of less than 1 cm between the tumour and the cut edge, compared with 28 per cent of the short-term survivors.

Among the 720 patients in the study, 227 received an adjuvant chemotherapy after liver resection. There was an association with survival of borderline significance, but the protocols used varied widely concerning timing in relation to operation, route of administration and drugs used; consequently no comparison could be made concerning the relative benefits of the various treatment modalities. However, 493 patients did not receive any adjuvant chemotherapy. In this subgroup, the rates for long- and short-term survivors were similar (61 and 70 per cent respectively).

Multivariate analysis

Three factors proved independently significant in multivariate analysis, and were associated with long-term survival: absence of serosa infiltration (odds ratio 2·0, 95 per cent confidence interval (c.i.) 1·3–2·8; $P = 0{\cdot}003$), absence of peritumoral lymph node invasion (odds ratio 1·6, 95 per cent c.i. 1·1–2·4; $P = 0{\cdot}04$) and liver resection margin of 1 cm or more (odds ratio 2·0, 95 per cent c.i. 1·2–3·4; $P = 0{\cdot}02$).

Discussion

The present study, based on the largest series available, shows that resection of colorectal hepatic metastases can result in long-term survival of more than 5 years. The limit of 5 years was chosen because, beyond this limit, the survival curve seems to plateau in most of the reported series. Such results have not been achieved yet by any other therapeutic approach.

In the present series, as well as in others[1,8,10], age and sex had no influence on long-term survival, neither had the site of the primary tumour. Patients with the best chance of long-term survival were those with absence of spread to the serosa, perirectal fat or peritumoral lymph nodes. This raises the question of whether patients with high-stage infiltration of the primary tumour gain any benefit from resection of liver metastases. In fact, serosa infiltration and lymph node invasion reflect both the length of evolution of the primary tumour before diagnosis and its proliferative activity. Analysis of instability of DNA sequences, and of *p53* point mutation in the primary tumour cells, could help in understanding why among long-term survivors there are still some patients who present with initially bad prognostic factors[11,12]. In the series of Hughes *et al.*[13], for a given Dukes stage the survival of patients who underwent curative resection of hepatic metastases was comparable to that of those with the same Dukes stage without colorectal hepatic metastases.

The delay between treatment of the primary tumour and the appearance of liver metastases is a controversial prognosis factor. In the present study, the time that had elapsed between colorectal surgery and discovery of the metastases, whether short or long, had no influence on long-term patient survival, whereas several other retrospective studies have shown a difference in survival when metastases are discovered less than 1 year after colorectal surgery[13–15]. However, in the present study the cut-off for comparison was at 3 months after resection of the primary tumour, which may explain these different observations.

The number of metastases is also a controversial prognostic factor. The presence of four or more liver metastases did not appear as a negative factor with respect to length of survival. Another large retrospective study[2] found no significant difference in survival in relation to the number of metastases when the resection was radical. The site of the metastases did not influence prognosis, and many studies have confirmed these results[2,8,13,16,17], justifying an aggressive surgical attitude for both bilobar and unilobar metastases. However, clearance between the cut edge and the metastases of at least 1 cm of normal parenchyma has to be resected; the prognostic role of this factor has been reported by others[13]. In the present study, a margin greater than 1 cm was more frequent in long-term survivors. A high preoperative CEA level has been noted in many studies as a factor of poor prognosis, and a shorter survival rate has been observed in this situation[1,2,6,18,19]. In the present study, a trend towards shorter survival with increased CEA concentration was also observed.

However, even among long-term survivors, some patients present initially with factors of poor prognosis; this observation suggests that it is justifiable to undertake resection of colorectal liver metastases whenever it may be performed safely as a curative treatment, irrespective of poor prognostic factors.

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Surgical workshop

Lateral approach to balloon-aided laparoscopic preperitoneal inguinal hernia repair

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When employing the laparoscopic retroperitoneal approach for inguinal hernias it is critical to obtain a large space in the preperitoneal cavity. Balloons are useful tools for this purpose. Once the space has been created, however, further instrument dissection is needed which may prove difficult. A new technique that may facilitate this step of the procedure is presented.

Surgical technique

The patient is placed in a supine position. A 2·0-cm horizontal incision is performed infraumbilically. The incision is carried down to the anterior rectus sheath, which is also incised. The rectus muscle is retracted laterally. A balloon-tipped device (PDB; Origin, Menlo Park, California, USA) is inserted behind the muscle and in front of the posterior rectus sheath, and oriented perpendicularly to the muscle fibres, aiming laterally, parallel to a transverse axis (*Fig. 1*). An end-viewing telescope is introduced into the device while the balloon is being insufflated. Disruption of the aponeurotic fibres of the lateral edge of the rectus sheath at the level of the semicircular line of Douglas can be observed. At this level the iliac retroperitoneum (Bogros' space) is entered and dilated (*Fig. 2*).

After deflation, the balloon is reoriented towards the pubis and the prevesical space is dilated. Additional cannulas are then inserted and the procedure continued as usual[1].

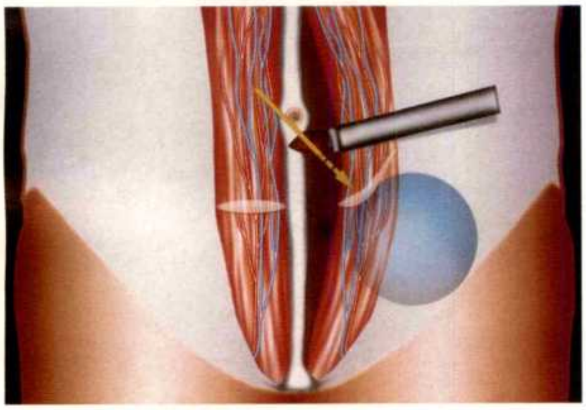

Fig. 1 Artist's impression of the space created by balloon inflation in the iliac retroperitoneum. After incising the skin and the anterior rectus sheath through an infraumbilical incision just off the midline, the rectus muscle is retracted with an army navy retractor. The arrow points towards the direction of introduction of the balloon-tipped device. Note the upwards displacement of the line of Douglas (pink)

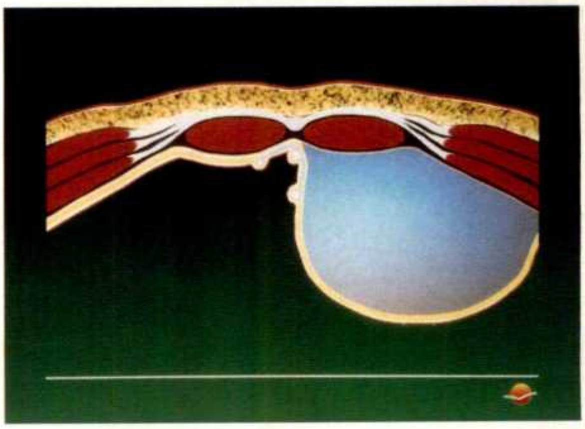

Fig. 2 Cross-section of the abdomen below the umbilicus showing the space created by balloon inflation posterior to the rectus and oblique muscles, and deep to the transversalis fascia in Bogros' plane

Discussion

Totally extraperitoneal laparoscopic hernioplasty is safe and reliable[2]. However, it is technically more demanding than the transabdominal approach because of the anatomy, which, in the absence of typical landmarks, is unclear to many surgeons.

The prevesical space can be dissected readily[3], but lateral dissection, starting between the epigastric vessels and the spermatic cord, is more difficult. At this stage of dissection there is a definite risk of bleeding from the epigastric vessels as well as of tearing of the peritoneum (especially in the presence of an appendicectomy scar). In contrast, the technique described here deals safely with both Retzius' and Bogros' spaces in a few minutes. Epigastric bleeding is avoided as dissection is performed deep to the vessels. Appendicectomy scars are contoured by the two balloon dissections.

Dissection of the indirect sac is the only remaining step, and a mini-anterior dissection, as described elsewhere, can be performed if desired[4].

This approach is quick, reliable, reproducible and teachable. It was used successfully without morbidity in 50 consecutive patients (48 men, two women) between September 1995 and March 1996. Median age was 58 (range 30–83) years. Six patients had had an appendicectomy. Some 58 hernias were treated (30 direct, 28 indirect); three were recurrent hernias. No perioperative or postoperative complications have occurred so far.

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Hernia repair in elderly patients

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Background This study evaluates a 5-year experience of the management of the most frequent abdominal wall hernias in an elderly population.

Methods From April 1990 to December 1995, 231 inguinal, 12 femoral and seven umbilical hernias were repaired in 221 patients (mean age 74 (range 66–93) years). Concomitant diseases were present in 157 patients. A mesh repair was performed with 'tension-free' or 'plug' techniques in all but 23 inguinal and two femoral hernia repairs, in which the Bassini or Shouldice procedures were adopted. Ten emergency hernia repairs were performed for strangulation. A total of 232 operations, including four emergency hernia repairs, were carried out under local anaesthesia.

Results There was no perioperative mortality. Acute intestinal bleeding occurred 2 days after surgery in a patient with colonic diverticular disease. Urinary retention occurred once following emergency hernia repair under general anaesthesia and twice after elective hernia repair under local anaesthesia. Local complications included four scrotal haematomas (2 per cent), three wound infections (1 per cent) and one case of orchitis with atrophy after repair of a recurrent hernia. There was one recurrence after a Bassini repair and one after Shouldice inguinal herniorrhaphy. No recurrence was observed after mesh repair.

Conclusion Local anaesthetic mesh hernia repair is safe and effective in elderly patients. Age should be no bar to elective hernia repair. This policy should avoid the complications of emergency operation.

Inguinal and umbilical hernias are common in the elderly because of loss of strength of the abdominal wall[1–3] and conditions which increase intra-abdominal pressure[4]. Elderly patients have a higher risk of complications and death following surgery because of the frequency of concomitant diseases. The proportion of elderly in the population is increasing so this study evaluates a 5-year experience of the management of the most frequent abdominal wall hernias in a geriatric population, principally using local anaesthetic techniques.

Table 1 Surgical techniques adopted for hernia repair

	Inguinal		Femoral		Umbilical
Repair	Unilateral	Bilateral	Unilateral	Bilateral	
Bassini	7	0	2	0	0
Shouldice	14	1	0	0	0
Preperitoneal*	2	3	0	0	0
Tension free*	155	19	0	0	3
Plug*	7	0	10	0	4

*With mesh

Table 2 Anaesthetic techniques adopted in the 250 hernia repairs

		Anaesthesia	
Hernia type	Operation	Local	General
Inguinal	Elective	213	12
	Emergency	2	4
Femoral	Elective	10	0
	Emergency	0	2
Umbilical	Elective	5	0
	Emergency	2	0

Patients and methods

Patients booked for elective hernia repair had preoperative evaluation consisting of routine blood tests, chest radiography and electrocardiography, and were admitted the day before, or on the day of operation. A more prolonged preoperative hospital stay was required only to treat concomitant diseases, or in patients undergoing additional major surgery.

Surgical procedures adopted for hernia repair are reported in *Table 1*. Early in the series the Bassini and the Shouldice procedures were used, followed later by 'tension-free' and 'plug' mesh techniques[5,6]. All bilateral inguinal hernias, as well as three inguinal with femoral and three inguinal with umbilical hernias, were operated on simultaneously. Preperitoneal inguinal mesh hernioplasty was performed in two patients in addition to right hemicolectomy and in three patients during elective abdominal aortic aneurysm repair. Other surgical procedures performed during hernia repair were three hydrocele operations and two orchidectomies. A suction drain was used in 33 cases following repair of inguinoscrotal or recurrent groin hernias and was removed after 24–48 h.

In most cases (*Table 2*) surgical repair was performed under local anaesthesia, consisting of block of the ilioinguinal and iliohypogastric nerves and infiltration of the surgical layers with a solution of 2 per cent mepivacaine, 0·5 per cent bupivacaine, 8·4 per cent sodium bicarbonate and saline. The concentrations of mepivacaine and bupivacaine were 60 mg and 15 mg per 10 ml of the solution respectively. The volume used ranged from 30 to 45 ml per hernia repair, depending on the thickness of the subcutaneous tissue and the size of hernia. About half of the anaesthetic solution was injected before making the skin incision and the rest in two to three steps during the operation. Premedication was performed in two-thirds of the patients with

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parenteral diazepam 0·14 mg/kg, and atropine 70 mcg/kg was used in half the cases. All chronically incarcerated and three strangulated groin hernias were operated on under local anaesthesia. Two patients, aged 93 and 87 years, with serious cardiopulmonary disease and a strangulated umbilical hernia also had surgery under local anaesthetic. In addition to hernia repair, a congested appendix in the former patient and 300 g of omentum contained in the hernia sac in the latter were removed. General anaesthesia with intravenous propofol 1·5 mg/kg was used temporarily in the second patient during omental resection. Intestinal resection was not necessary in any repair. The orchidectomies and hydrocele operations were accomplished under local anaesthesia. General anaesthesia was adopted in the other emergency operations, in selected elective repairs and in cases where a hernia was repaired during other major surgical procedures.

A urinary catheter was inserted before six emergency hernia repairs and in patients having major abdominal procedures. Antibiotics were not administered routinely.

Discharge of patients after elective hernia repair under local anaesthesia was scheduled for the same day or the day after operation. Patients received outpatient follow-up after 1 month and then yearly up to the fifth postoperative year.

Results

Between April 1990 and December 1995, 221 patients, 207 men and 14 women, with a mean age of 74 (range 66–93) years, had umbilical, inguinal or femoral hernia repair. Forty-nine patients were over 80 years old. Duration of the hernia ranged from 1 month to 22 years. Smoking, heavy alcohol consumption and constipation were reported in 63 (29 per cent), 38 (17 per cent) and 67 (30 per cent) respectively. Fifty-three patients with an inguinal hernia previously had a contralateral groin hernia repair.

Significant concomitant medical problems were observed in more than two-thirds of patients (*Table 3*). Thirteen were diabetic, and eight patients had chronic renal failure and were receiving continuous ambulatory peritoneal dialysis or haemodialysis. Five patients had been treated previously for a neoplastic disease and colonic cancer was detected before operation in two.

A total of 250 hernias were observed in the 221 patients. Fifty-six of the groin hernias were inguinoscrotal, 12 of which were huge. Fifteen inguinal hernias were chronically incarcerated and in ten cases (six inguinal, two femoral and two umbilical) the hernia was strangulated. There were 40 recurrent inguinal hernias.

Mean hospital stay after surgery was 1·8 days (range 3 h to 22 days); 101 patients (46 per cent) were discharged on the day of operation and 56 (25 per cent) the day after.

There were no perioperative deaths. Eight episodes of vagal stimulation with hypotension and/or bradycardia were recorded either during operation or in the first few hours after surgery but there was no correlation with the volume of anaesthetic solution used. An 81-year-old patient with colonic diverticular disease developed intestinal bleeding 2 days after elective inguinal hernia repair and required blood transfusion. Postoperative urinary retention developed in one patient following emergency inguinal hernia repair under general anaesthesia and in two patients following surgery under local anaesthetic.

Table 3 Concomitant medical conditions

	No. of patients
Cardiovascular	87 (39)
Urological	39 (18)
Gastrointestinal	30 (14)
Pulmonary	29 (13)
Neuropsychiatric	12 (5)
Renal	8 (4)
Neoplastic	7 (3)
None	64 (29)

Values in parentheses are percentages

Local complications consisted of one subcutaneous haematoma following umbilical hernia repair, four scrotal haematomas (2 per cent), three wound infections (1 per cent) and one infarction of the cord with orchitis after inguinal hernia repair. In the latter case of a recurrent hernia, testicular atrophy was observed after 1 month. Postoperative neuralgia was not reported.

Fourteen patients died 1–3 years following operation from unrelated diseases. The follow-up rate at 1, 2, 3 and 4 years was 89 per cent (184 cases), 90 per cent (105 cases), 80 per cent (54 cases) and 64 per cent (26 cases) respectively. Ten of the 23 patients were followed up for more than 5 years.

One recurrence occurred during the first year after operation following Bassini inguinal herniorrhaphy and one during the second year following Shouldice repair. No recurrence was observed in patients who had mesh inguinal hernioplasty; 150 of these patients (168 hernioplasties) were examined at 1 year and 76 (81 hernioplasties) at 2 years. At routine follow-up examination, 11 primary contralateral inguinal hernias and one femoral hernia were detected and subsequently treated.

Discussion

Because of the increased risk of postoperative complications in elderly patients, surgeons may be reluctant to perform elective repair of a reducible hernia. However, delay may increase the possibility of strangulation which necessitates surgery under adverse conditions, and an increased risk of morbidity and death[4,7–9]. Up to 40 per cent of hernia repairs, mainly inguinal and femoral, in older patients are performed for incarceration or small bowel obstruction[4]. In this experience, there were few emergency operations for strangulated hernia. Surgery was performed promptly as soon as symptoms of strangulation were evident and no intestinal resection was required. All patients had an uneventful postoperative course and were discharged within a few days of surgery, substantiating the notion that an acutely incarcerated hernia should be treated as soon as possible[8].

In geriatric patients, cardiovascular[8], pulmonary[10] and urinary[11] complications are frequent after hernia repair. The anaesthetic technique used has great importance. General and spinal anaesthesia are associated with higher rates of serious postoperative complications[10], including occasional postoperative death[7]. Local anaesthesia is seldom followed by major complications[10].

Most of these patients had a hernia repair under local anaesthesia, including all of those with chronically incarcerated hernias and four with strangulated hernias. Although more than two-thirds of the patients had one or more medical problems which increased the risk of operation, no major complications occurred either during or after surgery.

Urinary retention frequently occurs after either general or spinal anaesthesia[10,12–14]. In this series 39 patients had a history of prostatic enlargement or previous prostatectomy. Digital exploration of the prostate was not performed routinely but most of these elderly patients could have had a degree of prostatism without clinical symptoms. The two patients who developed urinary retention following hernia repair under local anaesthesia both had prostatic hyperplasia. These results are consistent with those reported by others[12,15], confirming the low incidence of urinary retention following local anaesthesia. Elderly men undergoing hernia repair under local anaesthesia generally do not require prophylactic drug treatment[16] and/or bladder catheterization.

As regards side-effects of local anaesthesia, hypotension and/or bradycardia during surgery or in the first few hours after operation was occasionally reported. These symptoms can occur following local anaesthesia[17] as well as other anaesthetic techniques[8]. However, no deaths or major complications due to vagal stimulation were seen. The incidence of hypotension/bradycardia in this series was lower than that observed in younger patients who had hernia repair in this institution and did not affect the postoperative course.

The lower incidence of major complications may be attributed to the early increase in mobility following local anaesthetic hernia repair[18,19]. The excellent short- and long-term results with mesh repair reported by others[20–23] have encouraged its routine use for all abdominal wall hernias in this department.

Local anaesthetic mesh hernia repair is safe and effective in elderly patients. With the exception of patients with a poor life expectancy, early elective hernia repair should be encouraged in elderly patients to avoid the increased risks of emergency surgery.

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Melanoma of the nose

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Background Melanoma of the nose is rare and management guidelines are poorly defined. In the past, excision margins have often been much narrower than for melanoma elsewhere.

Methods The study was a retrospective clinicopathological study of 34 patients with cutaneous melanoma of the nose treated in a single unit.

Results Desmoplastic neurotropic melanoma and lentigo maligna melanoma were the most common histological tumour types. Local recurrence occurred in eight patients, and in six cases appeared to be a result of inadequate excision margins. Regional lymph node metastases were associated with a very poor prognosis.

Conclusion Adequate surgical excision is the mainstay of successful treatment for melanoma of the nose. Excision margins for nasal melanoma should not be any less than for melanoma elsewhere. Careful planning is required, not only to gain local disease control and the best chance of cure, but also to achieve functionally and aesthetically acceptable results. Excision margins need not be compromised in view of the variety of local flaps that can be employed to close the primary defect.

Cutaneous malignant melanoma of the nose is rare. The planning of surgical treatment for melanomas in this region has in the past been influenced significantly by anatomical, functional and aesthetic considerations, with margins of excision tending to be considerably narrower than for melanomas in other areas of the body. In this paper, experience with cutaneous melanoma of the nose in a single unit is reviewed and important aspects of surgical therapy are discussed, particularly the use of local flaps to ensure that excision margins are not compromised.

Patients and methods

A retrospective analysis of a computerized database containing details of 9575 patients treated between July 1950 and June 1993 was undertaken. All patients with a primary malignant melanoma developing on the cutaneous surface of the nose were identified for study. The results presented include patients who received part of their definitive treatment at other centres before referral to the Sydney Melanoma Unit. Some clinical details relating to treatment and recurrence events not available in the database were obtained by hospital chart review or by communication with the patient's family physician. All available histology slides were reviewed by a single pathologist (K.A.C.).

Results

Between 1950 and 1993, 34 patients with cutaneous malignant melanoma of the nose were treated in this unit. This number represents 0·4 per cent of the total number of patients with melanoma treated during this period, and 2·0 per cent of patients with melanoma of the head and neck. Of the 34 patients, 24 received their entire definitive treatment at the Sydney Melanoma Unit. The remainder were referred for further management after having had part of their definitive treatment (i.e. after initial biopsy) at another centre.

The clinical and histopathological characteristics of the 34 patients with melanoma of the nose are reported in *Tables 1* and 2. The original histology slides for 20 of the patients were available for review. The male:female ratio for melanoma of the nose was 1:1, compared with a ratio of 1·5:1 for all head and neck melanomas treated in this unit. Twenty-two of the patients were over 60 years of age, with the maximum incidence in the eighth decade. This value is slightly higher than that for head and neck melanomas overall, where the maximum incidence occurs in the fifth decade. Clinically, none of the 34 patients had palpably involved cervical nodes at the time of initial presentation.

Histologically, desmoplastic neurotropic melanoma was the most common tumour type identified (ten patients).

Table 1 Clinical characteristics of 34 patients with melanoma of the nose

	No. of patients
Sex	
M	17
F	17
Age (years)	
< 20	0
20–29	1
30–39	4
40–49	3
50–59	4
60–69	7
> 70	15
Site	
Dorsal surface	9
Side wall	14
Tip	3
Alar	8

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Table 2 Histopathological characteristics

	No. of patients ($n = 34$)
Clark level	
1	4
2	5
3	8
4	8
5	6
Not known	3
Histology	
Superficial spreading melanoma	3
Lentigo maligna melanoma	7
Nodular melanoma	3
Desmoplastic neurotropic melanoma	10
Malignant blue naevus	1
Malignant melanoma not otherwise specified or classifiable	10
Thickness (mm)	
<0·76	5
0·76–1·49	9
1·50–3·99	10
≥4·00	7
Not known	3
Ulceration	
Yes	6
No	28

Table 5 Factors associated with recurrence

	No. of recurrences
Thickness (mm)	
≤0·75	3
0·76–1·49	2
1·50–3·99	0
≥4·00	2
Not known	1
Clark level	
1	1
2	1
3	1
4	3
5	2
Margins (cm)	
<1	4
1	3
2	1
Operation	
Local excision and primary closure	3
Local excision and graft	1
Wide excision and graft	2
Wide excision and flap repair	2

Table 3 Histological classification and tumour thickness

		Tumour thickness (mm)				
Histology	No.	≤0·75	0·76–1·49	1·50–3·99	≥4·0	Not known
Superficial spreading melanoma	3	1	1	1	—	—
Lentigo maligna melanoma	7	2	2	1	1	1
Nodular melanoma	3	—	1	2	—	—
Desmoplastic neurotropic melanoma	10	1	—	3	5	1
Malignant blue naevus	1	—	—	1	—	—
Unclassified	10	4	1	2	2	1

Table 4 Local treatment

	No. of patients ($n = 34$)
Operation	
Local excision and primary closure	7
Local excision and graft	5
Wide excision and graft	9
Wide excision and flap repair	13
Margins (cm)	
<1	12
1	11
2	11

This was followed by melanoma arising in Hutchinson's melanotic freckle (i.e. lentigo maligna melanoma), comprising seven of the 34 cases (*Table 2*). The relationships between histological classification and tumour thickness are detailed in *Table 3*. Local treatment details are shown in *Table 4*. All patients were treated with excision margins of 2 cm or less, and wounds were closed primarily or with a flap repair in 20 patients. A prophylactic modified radical neck dissection was performed in five patients, two of whom also underwent elective superficial parotidectomy. All five patients had negative nodes on subsequent histological examination. No disease recurred in the neck or parotid region following prophylactic lymph node dissection. However, one of these five patients subsequently developed distant metastases.

Local recurrence within the field of the primary site developed in eight patients, in half of the cases within 3 years (range 9–89 months). As expected, excision margins of 1 cm or less were associated with an increased incidence of local recurrence (*Table 5*). Two of the eight patients who developed local recurrence had a melanoma less than 1 mm in thickness and excision margins of less than 0·5 cm. In a further four patients who developed local recurrence, the tumours were more than 1 mm in thickness, but excision margins of only 1 cm were achieved.

Clinically palpable cervical nodes developed in five patients, all within 2 years (range 6–22 months). Four of these patients were treated by radical neck dissection. The remaining patient did not have a neck dissection because he was found to have systemic melanoma metastases, and died soon afterwards. Of the four patients who underwent neck dissection, two died from distant metastasis at 3 and 18 months, and one patient remains alive and well with no evidence of disease. The fourth patient developed metastases in the contralateral neck, for which another neck dissection was performed. He is alive and well with no evidence of disease 18 months later.

Radiotherapy was successful when administered for control of locally recurrent disease in five patients or as treatment for distant bony metastases in one patient. Chemotherapy and immunotherapy were used without demonstrable effect in four patients with systemic melanoma.

Distant metastatic disease developed in seven patients, with half of the metastases becoming apparent within 4 years (range 19–96 months). The most common metastatic sites were lung, brain, liver, skin and bone. Of this group, five patients died from melanoma, with a median survival of 37 months following initial treatment (length of follow-up 22–96 months). Four of the five patients had Clark level 4 melanomas, but the remaining patient, a 35-year-old man, had an *in situ* melanoma on the side wall of the nose which had been treated at another institution with a 1-cm excision margin and skin graft. This was followed by an ipsilateral prophylactic neck dissection (the reason for this is unclear) with histologically negative cervical nodes. The patient developed distant visceral metastases at 86 months and died from the disease 12 months later.

Of the remaining 29 patients, 23 are alive and well with no evidence of disease, with a median survival of 22 (range 3–265) months, and three are alive with melanoma (two with primary tumours that were desmoplastic–neurotropic in histological type and one that was non-classifiable). Three patients have died from causes unrelated to the melanoma.

Discussion

For patients with melanoma of the cutaneous surface of the nose (*Fig. 1*), particularly careful treatment planning is required, not only to gain local control of the disease but also to achieve the best possible chance of cure with minimal morbidity and disfigurement.

The clinical features of the cutaneous melanomas of the nose in this study were no different from those of melanoma at any other site. The percentage of the total experience with head and neck melanoma comprised by melanoma of the nose (2·0 per cent) was within the range of 1·8–4·3 per cent reported in other series[1–3]. Patients referred from outside the institution were a selected high-risk group because they comprised seven of the eight patients who developed recurrence and four of the five patients who ultimately died from the melanoma. An equal sex ratio was found in this study, whereas in a previous report Fisher[2] found a slight male predominance. The maximum incidence of melanoma of the nose in the eighth decade for patients in this study was at an older age than in Fisher's series.

The commonest histological tumour type identified in this series, desmoplastic neurotropic melanoma, comprised ten of the 34 lesions. The next most common group was lentigo maligna melanoma (seven of 34 cases). Lentigo maligna melanoma is an invasive melanoma arising in a lentigo maligna (i.e. Hutchinson's melanotic freckle). It occurs in sun-damaged skin. The reported incidence of invasive melanoma arising in Hutchinson's melanotic freckles at all sites ranges from 33 to 50 per cent[4,5]. Fisher's series of 36 nasal melanomas[2] had superficial spreading melanoma as the most common tumour type (17 of 36), compared with only three of 34 in the present series.

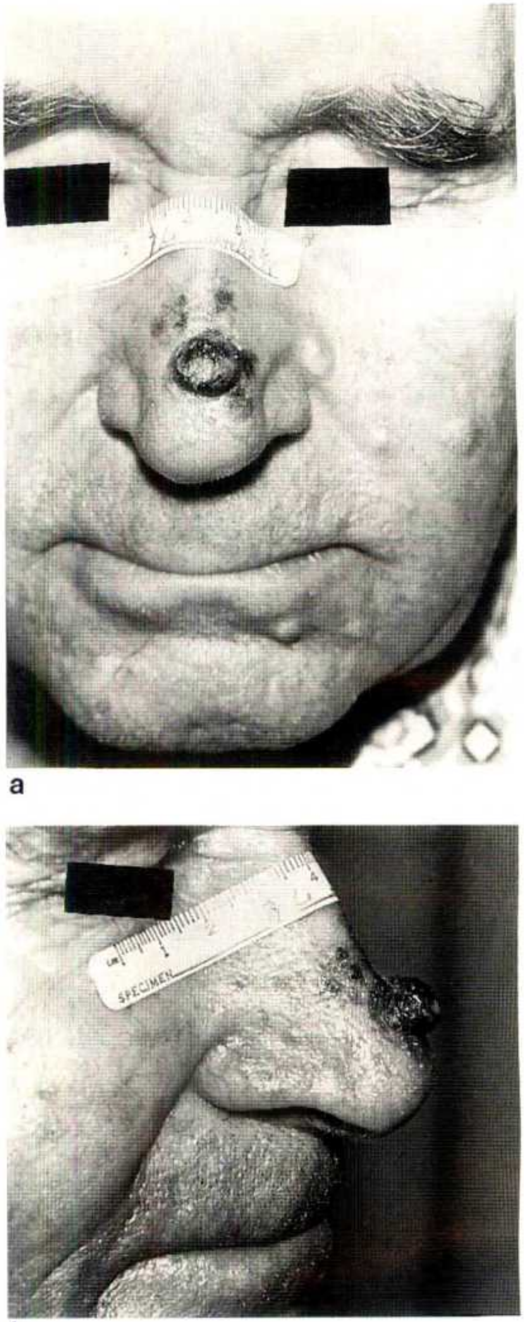

Fig. 1 **a** and **b** Patient with nodular melanoma on the dorsal surface of the nose

It was not possible to classify the tumour type for ten of the 34 melanomas in this series. That a proportion of melanomas cannot be easily classified into the main subtypes is well recognized[6], and nasal melanomas may have a somewhat higher proportion of unclassifiable tumour than melanomas at other sites.

Surgical treatment of melanoma of the nose is complicated by the need to preserve acceptable appearance, as well as function, without compromising disease control. Over half the present patients had primary closure or flap repair of the wound after excision; they all had excision margins of 2 cm or less. Tumour thickness, Clark level and extent of local treatment influence the incidence of local recurrence[7]. In this series, six of the eight patients with local recurrence had excision margins that must be regarded as inadequate (less than 0·5 cm for two tumours less than 1·0 mm in thickness, and less than 1 cm for four tumours greater than 1·0 mm in thickness). Local recurrence in these patients suggests that excision margins for melanoma of the nose should not be any less than for melanoma elsewhere on the body: for tumours less than 1·0 mm in thickness, a minimum excision margin of 1 cm, and for tumours greater than 1·0 mm in thickness, a wider excision with at least a 2-cm margin.

Flap reconstruction provides the most aesthetically satisfactory result and is the mainstay of repair of nasal defects. Excision should be planned with consideration of nasal subunits[8], which allows margins of at least 1 cm to be achieved. Multiple donor sites for flaps can be utilized if multiple subunits are excised. Commonly employed flaps include the forehead flap for the tip and dorsum of the nose and the nasolabial flap for the alar region[9,10]. Larger defects can be reconstructed with the Converse 'scalping' flap[11].

Apart from establishing clear margins, it is also important to achieve an appropriately deep excision plane. Nasal mucosa should be preserved wherever possible, keeping in mind that both bone and cartilage provide an effective barrier to local tumour spread. McGregor and McGregor[9] have pointed out that tumour fixation is slower to occur over nasal bone and lateral cartilages because of increased skin mobility over these structures, which overlap each other and are much thicker than alar cartilage.

The outlook for patients with nasal melanoma who have a Clark level 1 lesion at initial presentation but in whom spread to regional lymph nodes occurs later is poor, as evidenced by the fact that three of the five patients who developed regional lymph node metastases in this series died from melanoma within 18 months. Currently at the Sydney Melanoma Unit, patients who develop palpable node disease undergo a radical, modified radical or selective neck dissection[12]. Adjuvant radiotherapy may be given to patients who have multiple histologically positive nodes or extracapsular tumour spread. Although it is commonly considered that melanoma is not radiosensitive, radiotherapy can be effective if given appropriately, usually as a small number of large fractions[13].

In view of the relatively small number of patients in this series and the median follow-up time of only 36 months, no attempt was made to analyse survival outcome statistically. Fisher[2], however, reported no statistical differences in survival at 5 and 10 years for subsites within the head and neck region for 712 patients with stage 1 and 2 disease. For the nose, the survival rate for 33 patients with stage 1 lesions was 70 and 45 per cent at 5 and 10 years respectively.

Of some concern was the one patient in the present series with an *in situ* melanoma who died from the disease 96 months after receiving apparently adequate definitive treatment for the primary tumour. It seems unlikely that the *in situ* melanoma was the cause of the metastatic disease in this patient, especially in the presence of histologically proven negative lymph nodes on neck dissection. In this situation the possibility of an occult primary melanoma elsewhere cannot be excluded (the primary tumour having regressed or been removed previously without histological evaluation).

The time to first recurrence of a melanoma is dependent on tumour thickness, ulcerative state of the primary lesion, and whether or not the patient underwent regional lymph node dissection as part of the first definitive treatment[14]. In the present study, half of the locoregional recurrences and distant metastases occurred within 4 years. The frequency of review should therefore be modified to reflect this.

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Pilot study of carotid surgery for acute stroke

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Background Carotid endarterectomy is usually delayed for 2 months following an acute stroke, but the stroke may progress or a further stroke may occur. A randomized pilot study of urgent carotid surgery for acute stroke was undertaken to assess the feasibility of a definitive multicentre trial.

Methods Seven Manchester hospitals referred patients with acute stroke (less than 7 days previously), defined according to the Oxfordshire Community Stroke Project classification. The carotid arteries were examined by portable continuous-wave Doppler ultrasonography. Patients with more than 50 per cent carotid stenosis on portable Doppler ultrasonography underwent colour duplex Doppler imaging. Patients with more than 70–99 per cent carotid stenosis were randomized to urgent carotid surgery or best medical care.

Results A total of 593 patients were assessed over 2 years. Of these, 414 had acute stroke, of whom 380 had probable cerebral infarction. Complete ipsilateral internal carotid artery occlusion was most common in patients with total anterior circulation infarcts (33 (28 per cent) of 117), whereas severe ipsilateral (70–99 per cent) stenosis was most common in partial anterior circulation infarcts (25 (20 per cent) of 128). Only 16 patients (one total and 15 partial anterior circulation infarcts) were fit enough for surgery and consented to randomization.

Conclusion A definitive trial of urgent carotid surgery would need to screen large numbers of patients but could focus on patients with partial anterior circulation infarcts.

Carotid endarterectomy reduces the risk of subsequent stroke in patients following a transient ischaemic attack (TIA) or minor ischaemic stroke who have internal carotid artery stenosis greater than 70 per cent[1,2]. Surgery is usually delayed for 2 months following acute stroke. This is based on the belief that early surgery precipitates haemorrhage within the infarct, and follows poor reported results of urgent carotid surgery in the 1960s and 1970s[3–6]. However, computed tomography (CT) was not available then to exclude primary intracerebral haemorrhage. Furthermore, many of the patients were in 'coma, semicoma or stupor', and therefore presumably had large areas of infarcted brain beyond hope of recovery[5].

Interest in the potential role of urgent carotid surgery was renewed by reports of reduced neurological deficits in patients with progressing stroke and limited deficit[7–14]. These studies were encouraging, but were not randomized. A prospective randomized pilot study of urgent carotid surgery in acute stroke was established to assess the feasibility of a definitive multicentre trial.

Patients and methods

Patients with acute stroke

Patients were recruited from seven Manchester hospitals under the care of 44 consultant physicians. From March 1994 to January 1995, junior hospital doctors were asked to refer urgently all patients with a possible diagnosis of acute stroke. In February 1995 the protocol was amended so that patients were assessed only if the referring doctors considered that they might be fit for surgery.

Investigation and recruitment

A medically qualified stroke research fellow and a study coordinator (occupational therapist) assessed the patients at the referring hospital as soon as possible following referral. Acute stroke was defined as 'a sudden onset of acute neurological deficit lasting longer than 24 h assumed to be vascular in origin'. Patients assessed more than 7 days after the onset of stroke (late stroke) were ineligible for randomization. Focal neurological deficits lasting less than 24 h were classified as TIAs. Other presenting symptoms, such as dizziness and blackouts, were classified as 'not stroke'.

Patients with acute stroke were examined and categorized by means of the Oxfordshire Community Stroke Project (OCSP) classification, which divides patients according to symptoms and signs into anterior circulation infarct (either total (TACI) or partial (PACI)), lacunar infarct (LACI) or posterior circulation infarct (POCI)[15]. Patients with cerebral haemorrhage, as assessed by CT or the Siriraj stroke score, were excluded[16].

Carotid arteries were scanned by means of portable continuous-wave Doppler ultrasonography (Scimed Digidop Doppler 840S; Fishponds, Bristol, UK). Fit patients with a portable scan result suggesting more than 50 per cent carotid stenosis were transferred to the vascular studies unit for colour duplex imaging. Peak systolic Doppler frequency and real-time B-mode imaging were used to determine the severity of carotid artery stenosis. Criteria for diagnosing a complete occlusion were an absent Doppler signal, reduced diastolic flow in the ipsilateral common carotid artery, and flow reversal on the supraorbital Doppler test. Intra-arterial digital subtraction angiography (IADSA) was arranged if duplex studies were equivocal and the patient was fit for surgery.

Patients with a recent stroke (less than 7 days previously) and 70–99 per cent ipsilateral internal carotid artery stenosis on duplex imaging were considered for randomization to urgent surgery or best medical care (which included surgery at 2 months). Exclusion criteria were cerebral haemorrhage or intracranial space-occupying lesion on CT, and any medical condition that precluded surgery.

Carotid endarterectomy was performed as soon as it could be scheduled. Outcome was assessed at 7 days, 2 months and 6 months using well validated scores of neurological and functional recovery.

Results

A total of 593 patients were referred between March 1994 and February 1996, of whom 489 were referred before referral criteria were refined in February 1995. Clinical

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Table 1 Prevalence of ipsilateral carotid stenosis in the Oxfordshire Community Stroke Project subtypes of cerebral infarction

		Stenosis (%)				
	Unassessable*	0–49	50–69	70–99	Occluded	Total
TACI	4	68	6	6	33	117
PACI	3	74	9	25	17	128
LACI	0	96	8	1	3	108
POCI	0	24	2	1	0	27
Total	7	262	25	33	53	380

*Patients who were too restless to allow adequate Doppler signals to be obtained. TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; LACI, lacunar infarct; POCI, posterior circulation infarct. $P < 0\cdot001$ (χ^2 test)

diagnoses included 69 TIAs, 57 late strokes and 53 'not stroke'. Some 414 patients had suffered an acute stroke, of whom 34 had cerebral haemorrhage on CT or by Siriraj score. Categorization of the remaining 380 patients with cerebral infarction included 117 (31 per cent) TACIs and 128 (34 per cent) PACIs (*Table 1*). A total of 33 patients had 70–99 per cent carotid stenosis on duplex imaging.

There were 25 patients with PACI and severe internal carotid stenosis: 15 were randomized, two patients refused, randomization could not be achieved within 7 days in one (due to late referral), six were medically unfit for surgery and one had haemorrhagic transformation of an infarct on CT. Of the six patients with TACIs and 70–99 per cent stenosis, only one was medically fit for surgery and was randomized. The single patient with LACI and severe stenosis was also unfit for surgery.

Seven of the 16 randomized patients were recruited after the referral criteria were modified in February 1995, which was seven (7 per cent) of 104 patients referred. This compared with a recruitment rate of only nine (2 per cent) of 489 patients assessed during 'blanket' screening between March 1994 and January 1995 ($P < 0\cdot05$, χ^2 test). The median time between onset and randomization was 5 (range 1–7) days. Delays of 2 days in arranging transport from the referring hospital contributed in seven cases.

Seven of the 16 patients recruited to the study were randomized to urgent surgery and underwent carotid endarterectomy within 24 h. In two patients the internal carotid artery was virtually occluded by fresh thrombus extending distally through the base of the skull, even though colour duplex ultrasonography in one and IADSA in the other had shown a patent internal carotid artery with intraluminal thrombus. Attempts at endarterectomy were unsuccessful and the carotid artery was ligated in both cases. Of the other five patients who underwent urgent carotid endarterectomy, one suffered transient neurological deterioration after operation. Another patient died 6 weeks after randomization. No autopsy was performed. The remaining three patients had no postoperative complications.

Of nine patients randomized to best medical care, one continued to have TIAs, and carotid surgery was carried out early at 6 weeks. In one patient, the stroke extended 5 days after randomization, with colour duplex studies showing progression of carotid artery stenosis from 90 per cent more than to 95 per cent with fresh thrombus. This patient underwent successful carotid endarterectomy at 2 months, as did one other patient in this group. One patient with evidence of fresh thrombus in the internal carotid artery was treated with intravenous heparin, and colour duplex imaging at 7 days showed no evidence of residual thrombus. The remaining five patients were reassessed in the outpatient clinic 2 months after randomization. Two refused surgery and two were still having rehabilitation; it was considered that surgery would delay their recovery. The 80 per cent stenosis in the final patient had remodelled to 55 per cent. Statistical analysis of neurological and functional recovery at this stage was inappropriate.

Discussion

The aim of this study was to assess the feasibility of a definitive trial by investigating the number of patients with acute stroke who might be suitable for carotid surgery, and to assess the practicalities of transferring patients to a tertiary referral centre.

Initially, every patient referred was assessed but only 2 per cent were suitable for randomization. Subsequently, when only patients with stroke judged fit for surgery were assessed, the total number of referrals fell but a higher proportion (7 per cent) were eligible for randomization.

Severe carotid artery stenosis was found in 20 per cent of patients with PACI, which was higher than in the other OCSP subtypes. Five per cent of patients with TACI also had severe stenosis, but most were not fit for surgery owing to the severity of the neurological deficit. These patients probably correspond to those described in the early studies of carotid surgery for acute stroke who were in 'coma, semicoma or stupor'[5].

The aim was to randomize patients as soon as possible following stroke onset, but the median time between stroke and randomization was 5 days. Difficulties in arranging transport and delays in referral contributed to this. As magnetic resonance imaging has demonstrated continuing neuronal loss for up to 7 days, carotid surgery after 5 days may still reduce neuronal loss in the ischaemic penumbra, but earlier surgery would presumably be advantageous[17].

Severe stenosis was most common in patients with PACI. Therefore, a definitive trial with a reasonable recruitment rate would most easily be accomplished by focusing on this subset. The main aim of urgent surgery in PACI is to prevent early stroke recurrence or progression due to further cerebral emboli. A definitive trial would need to recruit many more patients. The authors are now approaching major vascular units to determine potential support for a multicentre trial.

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Cells are present in the smoke created during laparoscopic surgery

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Background The application of laparoscopy for malignancy has been halted in many centres because of a growing number of reports of metastases arising in port sites. The smoke created by coagulation during laparoscopic surgery appears to contain particles visible to the naked eye. This study tested the hypothesis that whole cells can be carried as an aerosol in the pneumoperitoneum during laparoscopy.

Methods Nine patients undergoing laparoscopic surgery for benign and metastatic disease were studied. Throughout the procedure the gas of the pneumoperitoneum was allowed to escape through a filter. The filters and tubing were washed, and washing solution was centrifuged and stained immunohistochemically to identify the cells. Three of the filters were also examined with an electron microscope.

Results Six of the nine samples contained cells. Clumps of whole cells were identified as mesothelial in origin; the electron micrographs showed many other cells stuck to the filter, which appeared to be blood and mesothelial cells but were not analysed further.

Conclusion The presence of whole identifiable cells carried in the pneumoperitoneum raises concerns for operating staff and could be a mechanism for tumour implantation. No malignant cells were found, but ethical considerations prevented intentional coagulation of malignant tissue.

The mechanism for development of trocar-site metastases is unclear. Several hypotheses have been suggested, including the possibility that the pneumoperitoneum itself may carry an aerosol of malignant cells[1]. These cells, carried in the gas, would be forced around the trocar sites by virtue of the positive pressure pneumoperitoneum. During laparoscopic surgery there is a constant leak of carbon dioxide around the trocars, since the seal is never absolutely tight. Loss of hundreds of litres is not uncommon particularly during lengthy procedures.

The pneumoperitoneum is usually invisible to the naked eye except when it fills with surgical smoke caused by coagulation. The smoke that clouds the operative field clears slowly as a result of the leaks, and occasionally one of the trocars is opened intentionally to evacuate the smoke. Concerns over the dangers of surgical smoke to theatre staff have led to a number of studies examining the contents of smoke created during open surgery. Anecdotal reports of verrucae developing in unusual sites such as the anterior nares of laser operators have been reported[2]. Papillomavirus has been found in wart vapour from a carbon dioxide laser and electrocoagulation[3] and, perhaps more disturbingly, Baggish *et al.*[4] found human immunodeficiency virus proviral DNA in laser smoke. Oosterhuis *et al.*[5] found viable mouse melanoma cells after coagulation with a carbon dioxide laser. Viable tumour cells have also been found in the plume from a neodymium laser[6]. Smoke particles collected during mammoplasties have been demonstrated to be mutagenic to the TA98 strain of *Salmonella* bacteria[7]. Little is known about the contents of smoke in laparoscopic surgery[8].

The pneumoperitoneum creates a different situation to that encountered in open surgery, since the smoke is kept moist, pressurized and concentrated. Even allowing for the magnification of the video screen, the smoke appears to contain some large particles, visible to the naked eye. In contrast to the slow diffusion of smoke during open surgery, the fumes during laparoscopic surgery are forced out in a concentrated jet by virtue of the positive pressure in the abdominal cavity. In this study, an attempt was made to detect and identify whole cells in the gas.

Patients and methods

Nine laparoscopic operations were studied, including two cholecystectomies, two colectomies for symptomatic diverticular disease, two biopsies of liver metastases (ovarian and colonic primaries), one Nissen's fundoplication, one highly selective vagotomy and one rectopexy. Electrocoagulation was used in all the procedures. The gallbladders and liver biopsies were extracted in a plastic bag to prevent spillage (Endocatch, Autosuture France, Elancourt, France). The mean duration of operation was 116 (range 40–180) min and the mean volume of carbon dioxide used was 285 (120–590) litres. During the procedure the pneumoperitoneum was allowed to leak out through a plastic cannula which was passed through a 5-mm trocar and acted as a chimney. The plastic cannula was attached to a filter (UGF 1; Pall Biomedical, St Germain en Laye, France) of 0·5 μm pore size. The pneumoperitoneum was maintained by the high-flow insufflator (Laparoflator; Storz, Tuttlingen, Germany). At the end of the procedure, the filter and the connecting tube, which contained variable amounts of condensation fluid, were rinsed with phosphate-buffered saline (pH 7·5). The liquid recovered was centrifuged to concentrate the cells and the cytospins were prepared for routine May–Gruenwald Giemsa staining. Additional cytospins were immediately fixed in acetone and air-dried to be used for immunohistochemistry.

Standard avidin–biotin–peroxidase complex methodology was performed using the following monoclonal antibodies: anti-creatinine kinase gp 56kd (Immunotech, Marseilles, France) diluted 1:50, antihuman leucocyte common antigen (DAKO, Glostrup, Denmark) diluted 1:50 and Antivimentin (DAKO) diluted 1:10 (Ref. 9).

Three of the filters were also studied with electron microscopy

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to look for any cells that were caught in the filter and unavailable for cytological analysis.

Results

Six of the nine samples yielded cells. The three samples that were negative were taken from short procedures that involved very little coagulation and smoke formation (two laparoscopic cholecystectomies and one laparoscopic liver biopsy for metastases).

The four cytospins that were used for immunohistochemistry demonstrated cells of mesothelial origin (*Fig. 1*). The yield of cells appeared to be associated with the length, amount of coagulation and difficulty of the procedure, although it was impossible to quantify reliably.

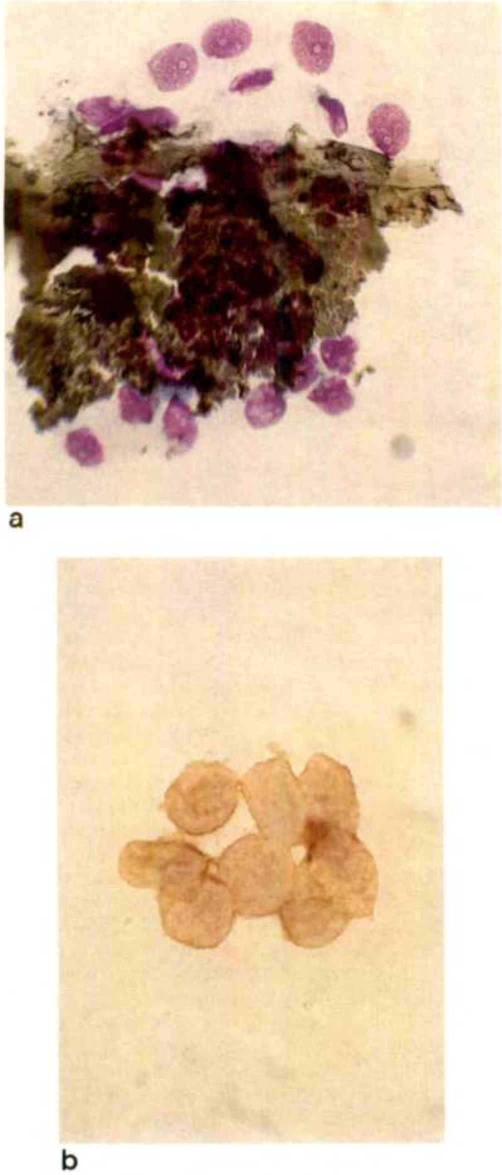

Fig. 1 Microscopy of centrifuged lavage of filters and tubing. **a** Slide showing carbonized debris and whole cells, identified morphologically as mesothelial in origin. **b** Cells stained positive for cytokeratin to identify their origin. (Images were similar for vimentin). May–Gruenwald Giemsa stain

Electron microscopy of three filters showed debris and identifiable cells stuck to the exposed side of the filter. These cells were not available for further identification, but appeared morphologically to be mesothelial and blood cells (*Fig. 2*).

All patients involved in the study made an uneventful recovery from surgery, and neither of the patients with malignant metastatic disease have developed cutaneous metastases at the time of writing.

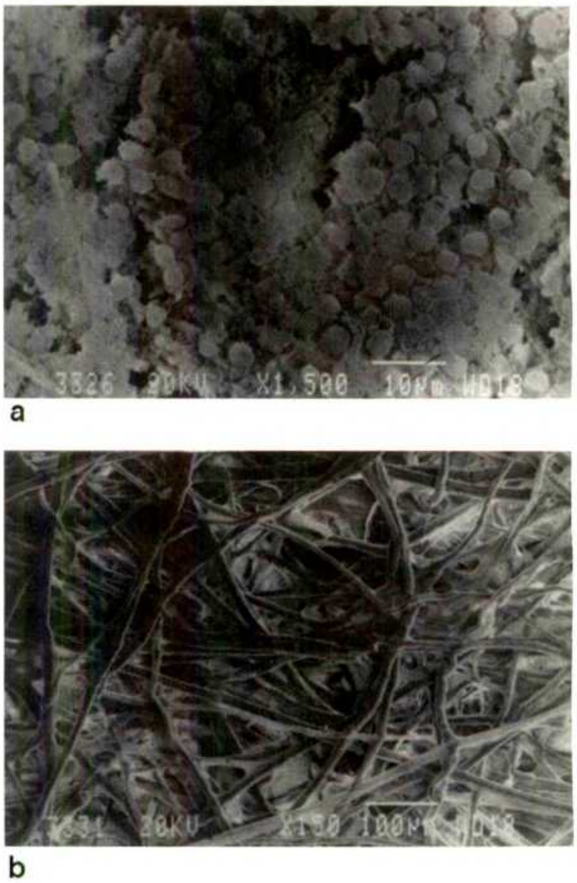

Fig. 2 Electron micrographs of the filters. **a** Side of filter exposed to the leaking gas from the pneumoperitoneum, showing adherent debris and whole cells. **b** Control view of the reverse side of the filter, showing that no cells have passed through. May–Gruenwald Giemsa stain

Discussion

This study has shown that free cells in aerosol form exist in the pneumoperitoneum, possibly liberated in the smoke caused by electrocoagulation. These cells can be carried with the gas that leaks out through an artificial chimney. Although the viability of the cells was not studied, they appeared to be whole and took up the cytochemical stains.

The physical characteristics of the pneumoperitoneum may help to preserve particles containing debris and cells, and may play a role in dispersing the aerosol of cells and concentrating them in the trocar wound[10]. During laparoscopic procedures, the pneumoperitoneum constantly leaks around the trocar sites. Cells carried in that gas would be naturally carried to the trocar sites, and could implant in the wounds if conditions were favourable. There may also be implications for the theatre staff if a fine aerosol of cells is carried to their mucous membranes during inadvertent opening of the trocar itself[11], although a surgical mask seems to prevent penetration of particles larger than 1 μm in an aerosol[12,13].

Metastases in trocar sites following laparoscopic surgery for malignant disease are most probably caused by direct implantation of tumour cells rather than haematogenous spread[14]. If this is the case, the tumour cells must be carried to the trocar site either during the procedure or during the healing period afterwards. In the present study no malignant cells were found in the filtered gas, but tumour was not being burned *in vivo* intentionally for ethical reasons. Animal studies are under way to see whether malignant cells can be dispersed similarly. During laparoscopic surgery for malignancy, neoplastic tissue can be burnt unintentionally, and malignant cells could be thus liberated.

Case reports and reviews of trocar-site metastases report an apparently random involvement of the wounds. It is not necessarily the wound which the specimen has been withdrawn through that is involved, but a trocar site some distance away[15]. A particularly leaky port insertion would tend to attract the cells carried in the escaping gas. The pressure may even force the cells to embed in fascial planes that act as protected environments for the malignant cells to grow in. Further work is needed to show any link between the aerosol of cells in the peritoneal cavity and trocar-wound metastases.

The high yield of cells in the smoke created during laparoscopic surgery is in contrast to the paucity of reports on whole cells in surgical smoke during open surgery[16]. There are no clear explanations as to why laparoscopic surgery for malignancy appears to be associated with a higher incidence of cutaneous metastases. The fine aerosol of cells carried in the pneumoperitoneum may provide some of the answers.

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Genetic instability in patients with metachronous colorectal cancers

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Background Nearly 7 per cent of patients who undergo resection for colorectal cancer develop metachronous cancers several years later. A molecular marker that could identify patients susceptible to metachronous cancers would be of clinical importance.

Methods Twenty-four colorectal cancers from 15 individuals with metachronous colorectal cancer were investigated for microsatellite instability at five loci by single stranded conformational polymorphism analysis. A control group of 14 colorectal cancers from individuals who had only developed one sporadic colorectal cancer each was analysed similarly.

Results Microsatellite instability was demonstrated in 17 of 24 cancers from individuals with metachronous cancer compared with one of 14 cancers from individuals with a single colorectal cancer.

Conclusion These results suggest that testing for microsatellite instability may be useful in recognizing patients at high risk of developing metachronous colorectal cancers.

In spite of new developments in surgical and oncological management of colorectal cancer, the 5-year survival rate for this disease has remained at almost 30 per cent over decades[1]. Nearly 7 per cent of patients with colorectal cancer develop new primary (metachronous) colorectal cancers[2]. Of these, 47 per cent are diagnosed at an advanced stage[3]. The ability to identify individuals susceptible to metachronous cancer might affect their clinical management leading to better prognosis.

Advances in molecular biology have shown that a subset of colorectal cancers harbour numerous genetic alterations which are particularly apparent in simple repeated DNA sequences known as microsatellite DNA[4]. This phenotype has been termed microsatellite instability or replication error and is almost always a feature of cancers from patients who have hereditary non-polyposis colorectal cancer (HNPCC)[5,6]. Individuals with HNPCC are predisposed to colorectal cancer because they carry an inherited mutation in one of four DNA mismatch repair genes known as *hMSH2, hMLH1, hPMS1* and *hPMS2*[7–10]. This leads to a dysfunctional DNA mismatch repair system in the cancers. The repair system functions to correct single base mismatches and alterations in microsatellite length that arise in DNA as a result of DNA polymerase slippage during replication. Defective mismatch repair can lead to a cascade of secondary mutations, some of which may affect oncogenes and tumour suppressor genes and therefore give rise to cancer[11,12]. Another DNA mismatch repair gene known as *GTBP* has been isolated recently, but no inherited mutations have yet been detected in it[13]. Patients with HNPCC are prone to developing both synchronous and metachronous colorectal cancers[14]. Colorectal cancers in young patients[15] and synchronous colorectal cancers[16] show microsatellite instability.

The aim of this study was to determine the prevalence of microsatellite instability in cancers of patients with metachronous colorectal cancer as a potential marker for the identification of high-risk individuals.

Materials and methods

Patient selection

A total of 24 colorectal cancers and corresponding normal tissue, fixed with formalin and embedded in paraffin wax, was obtained from 15 patients (eight women) with metachronous colorectal cancer. Ten first (primary) cancers and 14 subsequent (metachronous) cancers were investigated. Primary and metachronous cancers were studied from patients 1–8 but only the primary cancer in patients 9 and 10, and the metachronous cancer in patients 11–15. The mean age of the patients at onset of the primary cancer was 64·3 (range 49–82) years and for the metachronous cancer it was 69·8 (range 54–88) years. Right-sided cancers were defined as those from the caecum to the splenic flexure and left-sided lesions included those in the descending colon, sigmoid colon and rectum (*Fig. 1*). Seven of the ten primary cancers and four of the 14 metachronous cancers investigated were right sided.

A control group of 14 cancers and corresponding normal tissue from 14 patients (seven women) who had developed only one colorectal cancer each were also investigated. In three cases the cancers were in the right side of the colon (*Fig. 2*). The mean age of patients at cancer onset in this group was 72·6 (range 56–87) years. Ten of these pairs of cancerous and normal samples consisted of fresh tissue while the remaining four were from formalin-fixed paraffin-wax embedded tissue.

Patients with metachronous cancers had a minimum of 5 years' follow-up after the primary cancer and the control group of patients had been followed up for at least 2 years. None of the individuals in the study group or the control group had any family history of colorectal cancer.

DNA purification

Sections were made from each of the paraffin wax blocks and these were mounted on glass and stained with haematoxylin and eosin. Using the section as a guide, areas of cancer tissue and normal mucosa were marked out on the corresponding paraffin wax block. Cancer tissue and normal tissue were cut out from the

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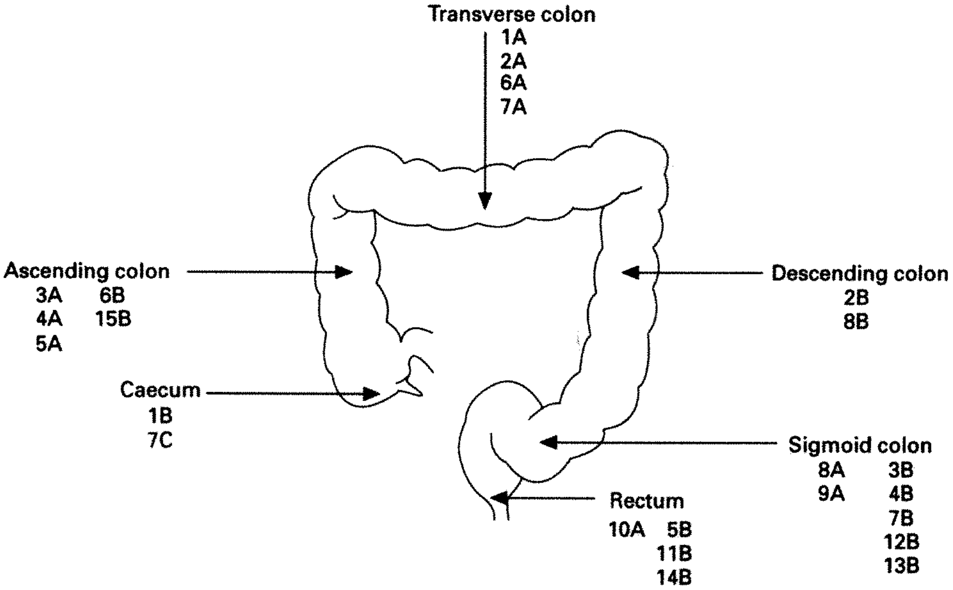

Fig. 1 Distribution of cancer in patients 1–15 with metachronous colorectal cancer. A, primary cancer; B and C, metachronous cancer

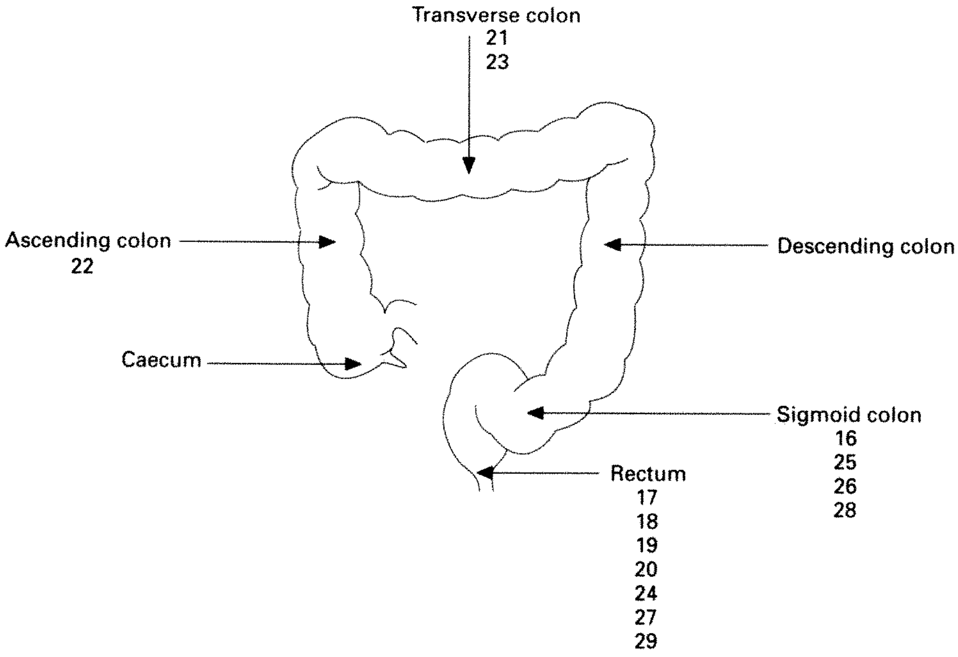

Fig. 2 Distribution of cancer in patients 16–29 with single colorectal cancer

paraffin wax block and placed into separate tubes. Paraffin wax was removed from the tissue using xylene and DNA was prepared from the samples following proteinase K digestion and phenol extraction[17].

DNA amplification

DNA was amplified at five different dinucleotide microsatellite loci (D2S123, D2S119[18], D5S346[19], D15S129[20] and D19S49[21]) using the polymerase chain reaction (PCR). Each PCR reaction mixture consisted of the following: 2′-deoxynucleoside 5′-triphosphates 0·2 mmol/l (Pharmacia, St Albans, UK); 1 × PCR buffer containing Tris-HCl 50 mmol/l (pH 9·0), KCl 50 mmol/l, $MgCl_2$ 7 mmol/l, $(NH_4)_2SO_4$ 16 mmol/l (HT Biotechnologies, Cambridge, UK); 0·5 units SuperTaq polymerase (HT Biotechnologies); 25 pmoles of each primer; and 200 ng genomic DNA. Sterile water was added to each mix in a 0·5 ml microfuge tube to make up to a uniform volume of 50 μl. Reaction tubes were placed in an Omnigene thermal cycler (Hybaid, Teddington, UK), denatured for 4 min at 94°C followed by 35 repeated cycles of 94°C for 30 s, the appropriate annealing temperature for 45 s and 72°C for 45 s. This was followed by a final elongation step at 72°C for 10 min.

Microsatellite instability assessment

Rapid single stranded conformational polymorphism (SSCP) analysis was performed on the Phastsystem (Pharmacia)[22]. PCR products were diluted up to tenfold with 95 per cent formamide. Following denaturation at 99°C for 10 min 2 μl of each sample was loaded on to non-denaturing 20 per cent polyacrylamide gels which had been prerun at 400 V, 10 mA, 2 W for 10 Vh at 15°C. Electrophoresis was then performed under the following conditions: 400 V, 5 mA, 2 W for 2 Vh at 15°C; 400 V, 10 mA, 2 W for 160–320 Vh at 15°C. Detection of DNA by silver staining was automated using the Phastsystem according to the manufacturer's instructions. Microsatellite instability in cancer tissue for a given primer set was defined as the appearance of new PCR bands either larger or smaller than those produced from normal mucosa.

Statistical analysis

The χ^2 test was used to determine significance of the microsatellite instability data.

Results

Fig. 3 shows a typical polyacrylamide gel of colorectal DNA amplified by PCR. The microsatellite instability data are summarized in *Table 1*. *Fig. 4* shows the distribution of the varying degrees of microsatellite instability in the patients with metachronous colorectal cancers. Detailed information of specific mutation sites is available from the authors.

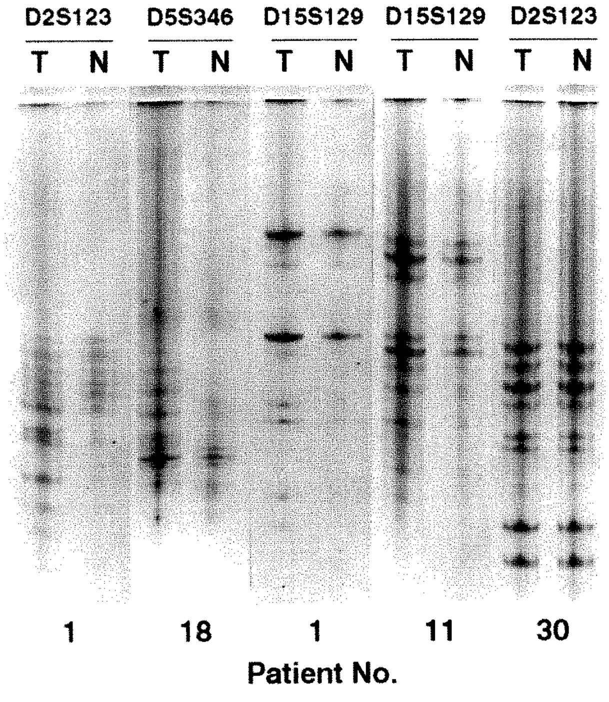

Fig. 3 Typical silver-stained polyacrylamide gels of PCR amplified colorectal cancer DNA (T) and corresponding normal mucosa (N). In patient 1, tumour DNA from the first primary colorectal cancer is shown for microsatellite loci D2S123 and D15S129. For Patients 18 and 11, tumour DNA from the second primary colorectal cancers are shown for microsatellite loci D5S346 and D15S129 respectively. These samples show microsatellite instability in tumour DNA which contains new alleles, not seen in corresponding normal mucosal DNA. The alleles are smaller in patients 1 (D2S123 and D15S129) and 11 (D15S129) and larger in patient 18 (D5S346). Patient 30 is in the control group and does not show microsatellite instability for D2S123 since the tumour and normal DNA share the same banding pattern

Table 1 Microsatellite instability in primary and metachronous cancers in relation to cancer site

	Proportion of cancers with microsatellite instability		
	Right-sided cancers	Left-sided cancers	Total
Primary cancer	6 of 7 (86)	0 of 3 (0)	6 of 10 (60)
Metachronous cancer	3 of 4 (75)	8 of 10 (80)	11 of 14 (79)

Values in parentheses are percentages. Right-sided cancers are up to the splenic flexure

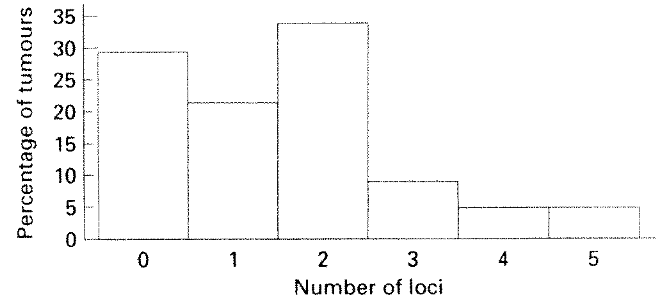

Fig. 4 Distribution of microsatellite instability in metachronous colorectal cancer. Graph shows percentage of metachronous tumours in relation to the number of loci showing microsatellite instability

Metachronous group

Paired primary and metachronous cancers (patients 1–8). Eight patients from the metachronous group (patients 1–8) could be investigated for each of their cancers and, of these, six (patients 1–6) showed microsatellite instability in both the primary and metachronous cancers. All six of these patients had primary cancers that were right sided which showed microsatellite instability involving two or more loci. The metachronous cancers from these six patients showed microsatellite instability but in three cases (patients 2, 3 and 6) only one locus was involved. Four of six of these metachronous cancers were left sided (patients 2–5). The remaining two individuals (patients 7 and 8) who had primary cancers in the right and left colon respectively, did not show any microsatellite instability in either the primary or metachronous cancers.

Primary cancer only (patients 9 and 10). Both of the primary cancers from these patients were left sided and neither showed microsatellite instability. Patient 9 was known to have developed a metachronous cancer in the rectum and patient 10 had one in the right colon. DNA could not be successfully extracted from paraffin wax-embedded tissue from either of these metachronous cancers.

Metachronous cancer only (patients 11–15). DNA could not be isolated from the primary cancers from patients 11–15. All the metachronous cancers from these patients showed microsatellite instability, and microsatellite instability was detected in at least two loci in the metachronous cancers from patients 11–13. In patients 11–14 the metachronous cancers were left sided and these patients were known to have had right-sided primary cancers. Patient 15 had a right-sided metachronous cancer and was known to have had a left-sided primary cancer.

In summary, therefore, microsatellite instability was detected in 17 of 24 cancers from 11 patients with metachronous colorectal cancer (patients 1–6 and 11–15) and half of these cancers showed instability at two or more of the loci investigated. Ten primary cancers from the metachronous group of patients were investigated (patients 1–10), of which seven were in the right side of the colon (patients 1–7), and six showed microsatellite instability (patients 1–6). The three primary cancers that were left sided from patients with metachronous disease (patients 8–10) did not show microsatellite instability. Fourteen metachronous cancers were investigated (patients 1–8 and 11–15), of which 11 showed microsatellite instability. Four of these cancers were right sided (patients 1, 6, 7 and 15) and three of them showed instability (patients 1, 6 and 15). Ten left-sided metachronous cancers were investigated (patients 2–5, 7, 8 and 11–14) of which eight showed microsatellite instability (patients 2–5 and 11–14).

Control group (patients 16–29)

Only one of the 14 cancers from the control group (patient 26) was found to be unstable. This was a left-sided cancer and showed microsatellite instability at only one locus.

The difference between the metachronous cancer and control groups was highly significant ($\chi^2 = 14{\cdot}37$, 1 d.f., $P = 0{\cdot}0002$).

Discussion

In this study the frequency of microsatellite instability was investigated in 24 colorectal cancers from 15 individuals with metachronous colorectal cancer. It was found that 17 of these cancers showed microsatellite instability. Microsatellite instability in a control group of patients who had only one colorectal cancer each occurred in only one of 14 cases. Other studies involving large numbers of patients (range 90–181 patients) have shown that the frequency of microsatellite instability in sporadic colorectal cancers in the general population is between 16 and 28 per cent[23,24] which is similar to the value of 7 per cent for the small number of patients with sporadic disease used as the control group of this study. These control patients therefore serve as a reasonable laboratory control for the methodology used.

The difference in the prevalence of microsatellite instability between cancers from the metachronous group of patients and cancers from the control group in this study is statistically significant. Although the longer follow-up time for the metachronous group of patients in this study may appear to bias against the control group, the difference in prevalence of microsatellite instability between the patients with metachronous cancer and that of published data[24] for sporadic colorectal cancer in the general population is still statistically significant (71 *versus* 28 per cent; $\chi^2 = 15{\cdot}10$, 1 d.f., $P = 0{\cdot}0001$). Metachronous colorectal cancers are rare in the general population, and patients from families with HNPCC develop metachronous lesions four times more often than patients with sporadic cancers[25]. Since the published frequency for microsatellite instability in sporadic colorectal cancers specifically excludes all patients who have a family history that conforms to HNPCC, it is justified to compare the frequency of microsatellite instability from this study for metachronous colorectal cancer with that of large studies of sporadic colorectal cancers[24].

Six individuals with metachronous colorectal cancer were positive for microsatellite instability in the primary cancer in this study. In eight patients from the metachronous cancer group consistency between primary and metachronous cancer was confirmed, whenever the primary cancer showed microsatellite instability, the metachronous cancers also showed microsatellite instability. This therefore implies that testing the primary cancer for microsatellite instability could predict the development of metachronous colorectal cancer.

Microsatellite instability has been detected in almost all colorectal cancers of patients with HNPCC[26]. These individuals develop colorectal cancers that are usually right sided and carry inherited mutations in one of four DNA mismatch repair genes (*hMSH2*, *hMLH1*, *hPMS1*, *hPMS2*)[7–10]. These cancers show a high level of microsatellite instability in that it is usually apparent in most loci investigated[27]. Although seven of ten of the primary cancers from the group of patients with metachronous colorectal cancer were right sided, most of the cancers in this study had a low level of microsatellite instability only involving one or two loci (*Fig. 4*). The data indicate that the pattern of microsatellite instability observed in this study is not only due to a difference in the biology in the left and right side of the colon. This is because the majority of metachronous cancers were left sided (possibly because the right colon was removed when the primary cancer was resected) and eight of these cancers showed microsatellite instability. Also, the only cancer to show microsatellite instability in all loci investigated was left sided. It is interesting to note that the only cancer from the control group that showed microsatellite instability was in the left colon. Thibodeau and colleagues[24] have shown that 87 per cent of sporadic colorectal cancers with microsatellite instability are right sided but only 35 per cent of right-sided colonic cancers show microsatellite instability.

Since none of the individuals fulfilled International Collaborative Group criteria for HNPCC[28] (three relatives affected with colorectal cancer in at least two generations, with at least two affected members being related through first degree and one colorectal cancer diagnosed before the age of 50), the incidence of microsatellite instability found in this study may be due to genes other than those currently identified for HNPCC. A high level of microsatellite instability has been detected in colorectal cancers from patients under the age of 35[15] regardless of their HNPCC status, also indicating the possible involvement of other causative genes. Colorectal carcinoma cell lines that express varying degrees of microsatellite instability have been identified[29]. Analysis of these cell lines has shown that mutations involving *GTBP*[30] (another DNA mismatch repair gene) and DNA Polymerase δ result in a relatively low level of microsatellite instability[31] similar to that detected in tumours from some of the patients with metachronous cancers in this study (*Fig. 4*). A low level of microsatellite instability has also been identified in some patients with multiple primary cancers[16].

This study demonstrates that microsatellite instability is a common feature of cancers from patients who develop metachronous colorectal cancers. It can be detected in 60 per cent of primary cancers from these patients, and the presence or absence of microsatellite instability is consistent in all cancers from each patient. These findings suggest that microsatellite instability may be a useful marker for identifying individuals who are at high risk of developing metachronous colorectal cancer. Although hereditary defects in genes associated with DNA mismatch repair may be found to be ultimately responsible for the development of metachronous colorectal cancer, testing for them is not practical at present because it would require the analysis of many genes. SSCP analysis for microsatellite instability using the Phastsystem is a rapid non-radioactive PCR-based system that is highly sensitive and reproducible. This technique may have a role in screening for patients at risk of metachronous colorectal cancer.

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Case report

Calculi within an anal fistula tract

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Stone formation within a fistula *in ano* tract has not been reported previously. A patient in whom multiple stones and a water melon seed were discovered within a fistula *in ano* tract during surgery is described, and the pathogenesis discussed.

Case report

A 62-year-old male farmer from Northern Sudan presented with anal pain of 10 years' duration. The pain increased with defaecation and occasionally prevented him from sitting. Initially he noticed a hard nodule in the anal canal, which was mobile and could be pushed inwards. The nodule later increased in size and its mobility became restricted. Seven months before presentation the man noted an offensive, sometimes bloody discharge with itching in the perianal region. An anal fistula and anal skin tags then developed. He had bright red rectal bleeding. Constipation was a constant feature.

Examination of the anal region revealed multiple skin tags, anal warts and a perianal fistula. On examination the rectum was tender and proctoscopy was not possible. Serum and urinary calcium and phosphate levels were normal.

Under general anaesthesia, sigmoidoscopy revealed the inner opening of the fistula. Anal dilatation, excision of the skin tags and fistulectomy was performed. Calculi and a water melon seed were found within the fistula tract. The calculi were 1·5 and 0·5 cm in diameter (*Fig. 1*). Postoperative recovery was uneventful.

Histopathological examination of the fistula tract showed mild chronic inflammation. Chemical analysis revealed the calculi to consist of calcium phosphate and magnesium carbonate.

Discussion

The successful treatment of a fistula *in ano* requires knowledge of the anatomy of the region and the pathogenesis of the fistula. The majority of fistulas are due to non-specific infection of the anal glands[1]. Specific causes must be excluded, in particular Crohn's disease, carcinoma, tuberculosis and trauma[1,2].

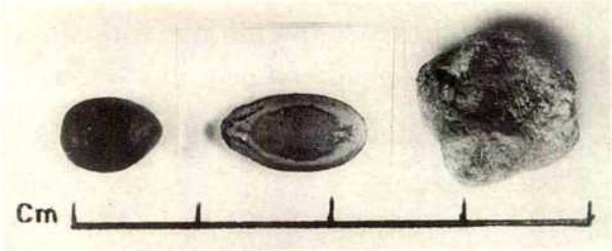

Fig. 1 Calculi and a water melon seed found within the fistula tract

Calculi in tissues are often silent; however, they may produce clinical effects[3]. The reason for stone formation in this fistula tract is unclear. The calculi were not gallstones as the biliary tract was ultrasonographically normal, or faecoliths as the stones were chemically similar to those encountered elsewhere in the body.

Calcium salt deposition in the tissues can occur as metastatic or dystrophic calcification[4]. Metastatic calcification is the deposition of calcium in soft tissue which is not the site of previous damage and is associated with hypercalcaemia. This is not applicable here as serum calcium and phosphate levels were normal. Dystrophic calcification is the deposition of calcium salts in injured, degenerating or necrotic tissue, with normal serum calcium levels. In this patient, infected tissue within the fistula may have become a nidus for secondary calculus formation. Its growth could have been facilitated by high levels of phosphate and low carbon dioxide in the injured tissue, leading to calcium deposition[4]. It is conceivable that these stones may have formed *in situ* by dystrophic calcification.

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Surgical workshop

Simultaneous treatment of faecal and urinary incontinence in children with spina bifida using double dynamic graciloplasty

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Patients with spina bifida have impaired control over anorectal and bladder function, leading to faecal and urinary incontinence. A wide range of conservative and surgical treatments exists. However, 53 per cent of patients have faecal soiling and long-term results show that only 24 per cent become fully continent to faeces and urine[1].

In patients with intractable faecal or urinary incontinence, good results have been described by the creation of a new anal or urinary sphincter using dynamic graciloplasty[2,3].

Patients with spina bifida, who do not respond to other treatments and are severely socially handicapped but seem to have good anorectal sensation and/or motility, could be treated with a combination of both techniques.

Surgical technique

Stage 1

The neurovascular bundles of the gracilis muscles were isolated proximally. Therefore the muscles remained vital when they were mobilized and detached distally. One gracilis muscle was transposed around the anal canal and the other was passed through the genitourinary diaphragm and wrapped around the bladder neck (*Fig. 1*). To improve bladder capacity and compliance a clam ileocystoplasty was performed. A 15-cm segment of ileum was isolated and bowel continuity was restored. The bladder was opened from one ureteral orifice to the other and bladder augmentation was achieved with the ileal segment, which was opened on its antimesenteric border.

Stage 2

Six weeks later, intramuscular electrodes (model 4300; Medtronic, Kerkrade, The Netherlands) were implanted in the vicinity of the obturator nerve branches in both gracilis muscles. Both leads were tunnelled subcutaneously and connected to a single neurostimulator (Itrel II, model 7424; Medtronic), which was implanted in the abdominal wall. Both electrodes were programmed as cathodes (negative poles), whereas the neurostimulator served as the anode (positive pole).

Training

Amplitude, rate, pulse width, polarity and duty cycle were programmed telemetrically by a physician. With an external magnet, the patient could switch the neurostimulator 'on' and 'off'. Before continuous stimulation was applied the graciloplasty was trained for 8 weeks according to a stimulation protocol[2]. Electrical stimulation caused the transformation of fast-twitch,

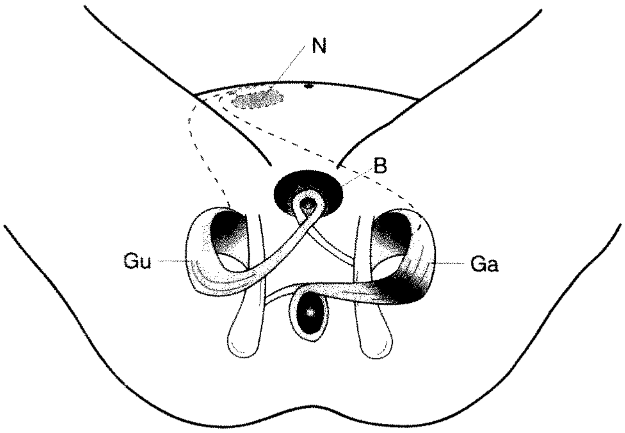

Fig. 1 Configuration of the double dynamic graciloplasty for patients with spina bifida and urinary and faecal incontinence. Gu, graciloplasty for re-creation of a urinary sphincter; Ga, graciloplasty for re-creation of an anal sphincter; N, neurostimulator; B, augmented bladder

Table 1 Patient details before and after double dynamic graciloplasty

			Bladder			Anal canal					
Patient no.	Age (years)	Follow-up (months)	UPP (mm/min)	UPP_{St} (mm/min)	Capacity (ml)	P_r (mmHg)	P_s (mmHg)	P_{St} (mmHg)	Sensibility (ml)	Urge capacity (ml)	RAIR
Before surgery											
1	17		30		254	83	83		20	80	+
2	13		29		250	59	69		20	70	+
After surgery											
1		12	40	50	450	66	159	130			
2		6	30	52	268	58	193	110			

UPP, Urethral Pressure Profile; UPP_{St}, Urethral Pressure Profile during electrical stimulation; P_r, resting pressure; P_s, voluntary squeeze pressure; P_{St}, pressure during electrical stimulation; RAIR, rectoanal inhibitory reflex

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fatigue-prone, type II fibres into slow-twitch, fatigue-resistant, type I fibres[4].

Discussion

This technique was applied in two young patients with spina bifida who had debilitating urinary and faecal incontinence and had failed conservative treatment (*Table 1*). Both patients had normal rectal sensation, which is essential for good outcome from any treatment for faecal incontinence[5]. In the first patient, the graciloplasty has produced normal resting pressures (stimulation switched 'off'), but he nevertheless requires enemas for rectal emptying. He is continent of urine. The second patient is continent of both urine and faeces.

The advantages of dynamic graciloplasty are that autologous material is used and a dynamic neosphincter created, consisting of contracting muscle. It allows normal closure and opening of the anus and bladder neck. The operation was well tolerated by both patients and no revision surgery was required. It remains hard to predict whether patients who have been incontinent all their lives will become constipated once an outlet barrier is created. Patients expected to develop constipation should not undergo dynamic graciloplasty. This new treatment can provide a solution in well selected patients who are severely socially handicapped, have good anorectal sensation and for whom no other possibilities are available.

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Short note

Timing of operation for appendicitis

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Surgical teaching has advocated early appendicectomy with the sacrifice of diagnostic accuracy to avoid the morbidity and mortality associated with perforation of the acutely inflamed appendix[1]. Both patient and hospital factors may lead to a delay in treatment and it has been suggested that patient factors are mainly responsible[2]; hospital factors have seldom been addressed.

Patients and methods

The time to presentation in the accident and emergency department, time to theatre following presentation and actual time of operation were reviewed in 275 patients who underwent appendicectomy between June 1993 and August 1995. Data were collected from computerized accident and emergency department and anaesthetic records and case notes. Duration of preoperative symptoms was based on patient recall, which was clearly documented in the majority of cases. In general, antibiotics were given when evidence of peritonitis existed, otherwise at the time of operation. Appendices were classified as normal, inflamed or perforated based on pathological findings. No attempt was made to quantify degree of peritonitis in those with perforated appendicitis. Hospital stay and complications were recorded. Results are expressed as mean(s.e.m.). Statistical analyses were by analysis of variance and the χ^2 test.

Results

A total of 193 patients (70·2 per cent) had an inflamed appendix (inflamed or gangrenous change) and 40 (14·5 per cent) had a perforated appendix (visible hole present); the rest were normal (15·3 per cent). The time to presentation in the accident and emergency department and time to theatre following admission were both significantly greater in those with a perforated appendix in comparison with the inflamed group (42·7(5·8) *versus* 31·0(2·5) h, $P < 0{\cdot}054$; 18·3(3·4) *versus* 13·5(0·7) h, $P < 0{\cdot}025$ respectively).

The proportion of patients within the inflamed and perforated groups undergoing operation was similar throughout the day (*Table 1*). Eighty-seven of 253 patients were identified as initially undergoing a 'wait and see' policy. Of these, 69, 11 and 20 per cent had an inflamed, perforated or normal appendix respectively, similar proportions to those in the overall group. All patients operated on between midnight and 06.00 hours had a shorter time to surgery than at other times during the day (9·9(1·3) *versus* 15·5(0·9) h, $P < 0{\cdot}015$).

Twenty (10·4 per cent) of 193 patients with inflamed appendicitis developed complications, compared with ten of 40 patients with perforated appendicitis ($\chi^2 = 6{\cdot}3$, 1 d.f., $P < 0{\cdot}01$). Complications were mainly prolonged pyrexia or ileus, wound infection and intra-abdominal abscess, all of which delayed discharge. Postoperative hospital stay was also significantly greater in the perforated group (139·7(11·3) *versus* 88·3(8·9) h, $P < 0{\cdot}008$).

Table 1 Timing of surgery in inflamed and perforated groups

Time	Inflamed	Perforated
Midnight to 06.00 hours	29 (15·0)	6 (15)
06.00 to 12.00 hours	27 (14·0)	7 (18)
12.00 to 18.00 hours	64 (33·0)	12 (30)
18.00 hours to midnight	73 (38·0)	15 (38)
Total	192 (100)	40 (100)

Values in parentheses are percentages. $\chi^2 = 9{\cdot}6$, 9 d.f., $P = 0{\cdot}38$

Discussion

Although this was a retrospective study, it is clear that the mean time to surgery for all patients was in excess of that in other reports[2,3]. The results, however, suggest that both late presentation and delay to surgery following admission are associated with perforated appendicitis and increased morbidity. However, as demonstrated in other studies an initial 'wait and see' approach does not increase the incidence of perforated appendicitis[4]; hence, other factors need to be considered. The major factors in delay to theatre following admission are likely to be a conscious or inadvertent decision to delay surgery taken by the surgical staff. Concerns regarding unnecessary or inadvisable emergency surgery following from the publication of the report of the Confidential Enquiry into Perioperative Deaths[5] influence this process. Despite this concern, 15·1 per cent of patients in this series were still operated on during night-time hours. Alternatively, difficulties may arise because of access to operating theatres for emergency cases; this is supported by the shorter time to surgery for patients operated on during the night.

This study emphasizes the importance of clinical audit of appendicitis, as morbidity and postoperative hospital stay continue to be greater in those with perforation. Although prospective studies may identify specific causes for delay to surgery in appendicitis, increased awareness during such studies may alter clinical practice. Attitudes amongst the surgical staff in prioritizing patients with appendicitis for surgery and access to emergency theatres may be the major factors that contribute to this problem and deserve further scrutiny.

Acknowledgements

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Surgical workshop

Tactile feedback in laparoscopic colonic surgery

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Laparoscopic surgery lacks the manual dexterity afforded at open surgery[1]. A dexterity arm (*Fig. 1*) allows the surgeon to place his or her hand and arm into the insufflated peritoneum and operate manually while pneumoperitoneum is maintained. The technique described below has been used for a low anterior resection.

Surgical technique

The patient weighed 140 kg and was 165 cm tall. She had a rectal tumour 6 cm above the dentate line. Following peritoneoscopy, the site in the left iliac fossa for the dexterity arm was chosen. A skin crease incision was made, according to the size of the surgeon's glove. A wound protector was inserted and rolled over an absorbent roll. This roll prevented any exudate from interfering with the adhesion of the dexterity arm plate to the skin. The surgeon, standing on the patient's left side, placed a 'pneumoarm' over his left arm; this was a sleeve of non-porous plastic, which prevents loss of gas through the operating gown. The dexterity arm was placed carefully around the wound protector and attached to the surrounding skin. The surgeon's arm was placed within the dexterity arm into the peritoneal cavity. The arm was secured tightly around the pneumoarm and surgeon's gown above the elbow with a Velcro (Pilling Weck, Le Faget, France) strap. Pneumoperitoneum was re-established.

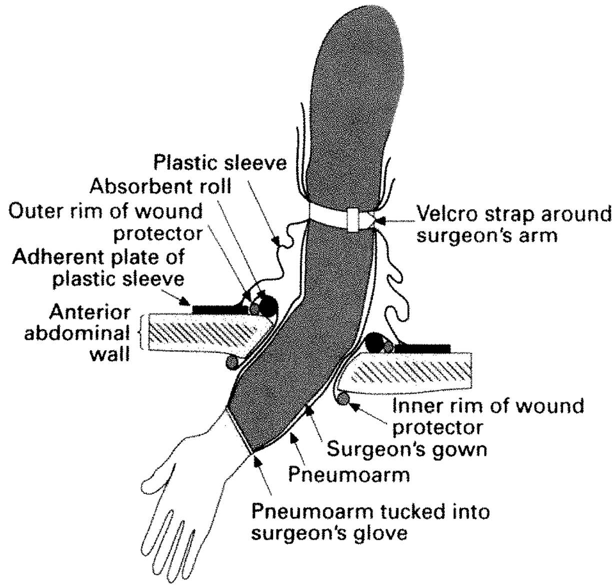
Plastic sleeve
Absorbent roll
Outer rim of wound protector
Adherent plate of plastic sleeve
Anterior abdominal wall
Velcro strap around surgeon's arm
Inner rim of wound protector
Surgeon's gown
Pneumoarm
Pneumoarm tucked into surgeon's glove

Fig. 1 Schematic diagram of the dexterity arm

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The liver was palpated; the tumour was identified and mobilized with the surgeon looking at the television monitor using conventional laparoscopic instruments with one hand and manipulating tissues with the other. The ureters were identified and the inferior mesenteric vessels were palpated and divided precisely with an Endo-GIA (Ethicon, Edinburgh, UK). The surgeon stood between the patient's legs and placed his right arm in the dexterity arm to mobilize the splenic flexure. The specimen was removed through the dexterity arm. The cross-stapled anastomosis was controlled with the hand in the abdomen. The incision was 8·5 cm long and the operating time was 150 min.

The patient passed flatus 2 days after surgery. She developed a urinary tract infection and was discharged on the ninth postoperative day.

Discussion

The dexterity arm combines the advantages of open surgery with those of laparoscopic surgery, as many of the difficulties encountered in laparoscopic colorectal surgery relate to the surgeon's inability to insert a hand into the peritoneal cavity[2]. The ability to feel tissues allows the surgeon to localize and assess tumour mobility and palpate the liver for metastases. Blood vessels can be identified by palpation within a fatty mesentery. Many laparoscopic grasping devices crush bowel wall; the dexterity arm enables the surgeon to apply sensitive non-crushing traction and countertraction. The intraperitoneal hand is able to manipulate tissues so that scissors and stapling devices are placed accurately, even when in relatively inaccessible sites. The surgeon is able to angulate his or her fingers around corners, and the tactile feedback from tissues and organs shown on the television monitors may increase the surgeon's confidence in dissecting tissues. The authors believe this simple technique may prove to be an advance in laparoscopic colorectal surgery.

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Management of blunt liver trauma in children

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Introduction Management of liver trauma in childhood represents a rare but formidable challenge.

Methods Clinical presentation, grade of liver injury and Injury Severity Score (ISS) were studied in 11 cases of blunt liver trauma to examine factors influencing outcome.

Results Seven of the 11 children were injured severely and had an ISS greater than 16. Seven who were haemodynamically stable were treated without operation, but four required surgery for grade III, IV and V liver injuries. Two children had primary repair of hepatic lacerations. Perihepatic packing was employed in two other cases (grade IV and V injury) for uncontrollable haemorrhage. Delayed debridement and thrombectomy plus vena cava repair with suturing of liver lacerations in these patients obviated heroic efforts at primary repair. Nine children survived. There were two deaths from head and neck trauma.

Discussion Selected children with liver trauma can be managed non-operatively using established trauma guidelines. Perihepatic packing is recommended in unstable patients with complex injuries, followed by delayed definitive repair.

Trauma is a leading cause of death and disability in children[1]. Abdominal trauma accounts for a substantial proportion of paediatric fatalities, frequently from liver injury[2,3]. The management of major liver injury in children is a formidable challenge. Prompt recognition and effective resuscitation form an integral part of initial management. Other reports often focus on urgent operation for children who sustain blunt liver injury[2]. The advantages of emergency laparotomy are the ability to assess solid organ and hollow visceral injury, together with the opportunity to expedite surgical repair[4]. However, clinically and experimentally, it has been shown that bleeding from the injured liver can cease spontaneously; hence strategies that advocate selective non-operative management have evolved[2,4–9]. Such a policy is possible because of improvements in resuscitation, intensive care and monitoring of trauma patients, coupled with advances in diagnostic radiology[10–13]. Computed tomography (CT) can accurately detect solid organ injury in abdominal trauma[10–13]. No comparative data are available on the current management of liver trauma in children from a major UK paediatric surgical centre. The present study was undertaken to evaluate recent experience in this hospital.

Patients and methods

Between January 1989 and December 1994, 11 consecutive patients with blunt liver trauma were managed at Alder Hey Children's Hospital. Children were evaluated clinically and resuscitated by a trauma team using Advanced Trauma Life Support (ATLS) guidelines[14]. All patients had plain radiography of the lateral cervical spine, chest and pelvis, followed by CT in those who remained haemodynamically stable. Abdominal CT was performed using a double-contrast technique[13]. Ultrasonography was employed only in the rare situation when CT imaging was not available. Patients with multiple injuries, such as head and chest trauma, had appropriate additional studies.

Children who were stable following initial resuscitation were admitted for close monitoring to a high-dependency general surgical ward or the paediatric intensive care unit, depending on the extent of injury and/or requirements for ventilatory support. Haemodynamically unstable patients who failed to respond to intravenous fluid resuscitation, or whose blood transfusion requirements exceeded 40 ml/kg, had emergency laparotomy[14].

An algorithm summarizing the trauma management is shown in *Fig. 1*. Peritoneal lavage was not employed. Liver injuries were graded in severity as outlined by the American Association for the Surgery of Trauma[15–17].

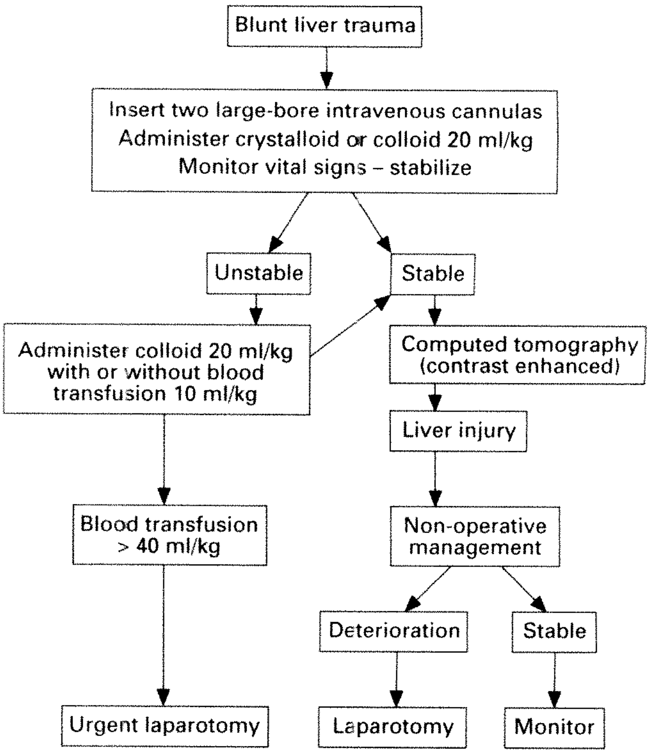
Blunt liver trauma
Insert two large-bore intravenous cannulas
Administer crystalloid or colloid 20 ml/kg
Monitor vital signs – stabilize
Unstable
Stable
Administer colloid 20 ml/kg with or without blood transfusion 10 ml/kg
Computed tomography (contrast enhanced)
Liver injury
Blood transfusion > 40 ml/kg
Non-operative management
Deterioration
Stable
Urgent laparotomy
Laparotomy
Monitor

Fig. 1 Algorithm for the management of paediatric blunt liver trauma

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Results

There were eight boys and three girls of median age 5 (range 3–13) years. Nine children sustained injuries following road traffic accidents. Eight of these were pedestrians; the other a motor vehicle passenger. One child was injured in a fall and the last suffered a crush injury to the liver after a metal vice from a workbench fell on to his abdomen. Liver injury was confirmed by CT in seven patients and in one by ultrasonography. Urgent laparotomy established hepatic injury as the source of bleeding and haemodynamic instability in the other three children.

The grade of liver injury and Injury Severity Score (ISS) are shown in *Table 1*. Seven patients had an ISS higher than 16 (mean ISS 30·3 (range 5–75)). Seven patients were managed without operation and four required operation. At exploration, two children had extensive hepatic lacerations sutured (grade III and V injuries), one of whom also had a torn left hepatic vein repaired. Laparotomy with full mobilization of the injured liver and temporary perihepatic packing was employed in two other patients with grade IV and V injuries (*Fig. 2*). In one of these children, who had a central hepatic laceration, delayed debridement was performed 24 h after the initial injury. Remaining bleeding points were easily controlled at this stage. The other child was transferred 48 h after stabilization to a supraregional hepatobiliary centre where thrombectomy, vena cava repair and suturing of hepatic lacerations was later performed.

Overall, nine children survived. Both deaths in the series were due to associated severe head and neck trauma (*Table 1*). No complications occurred in patients managed without operation.

Table 1 Liver injury profile

Grade of liver injury	No. of patients	Injury Severity Score
I	1	5
II	3	6, 19, 75*
III	3	14, 25, 34
IV	1	17
V	2	29, 34
VI	1	75†

*Patient died as a result of an associated brainstem injury; †patient died from diffuse cerebral oedema and high cervical cord injury

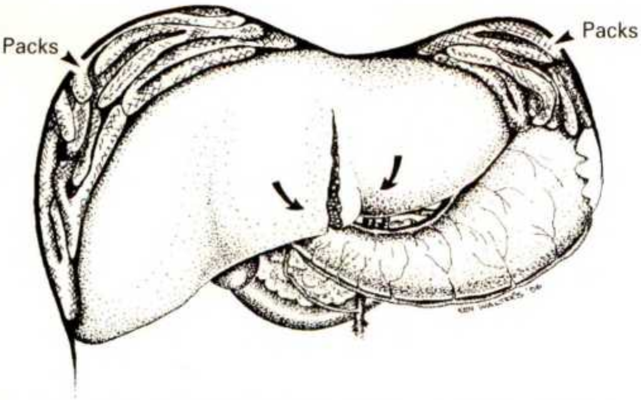

Fig. 2 Technique of perihepatic packing for central liver injury. Abdominal wound packs are placed around the superior and lateral surfaces of the liver to ensure effective tamponade

Discussion

Advances in diagnostic imaging, improved paediatric resuscitation and a better understanding of the pathophysiology of liver injury have led to strategies of non-operative management for blunt hepatic injury in childhood[2–13]. Subject to strict criteria, these results confirm that this is safe and effective in patients with less severe grades of liver injury who remain haemodynamically stable following volume resuscitation. These criteria may best be fulfilled in a paediatric surgical centre with an organized trauma system[18–20]. The small number of paediatric liver injuries treated in the authors' institution, with a catchment population of 3·2 million, over the 6 years of the study justifies centralization of trauma care facilities[19]. A recent analysis of paediatric trauma patients cared for by adult surgeons highlighted a 47 per cent laparotomy rate for liver and splenic injuries[18]. This may reflect extrapolation of the surgical principles of adult trauma care to children.

Unstable patients should have urgent surgery. These patients are easily defined with ATLS guidelines[14]. In the present series four children required laparotomy for significant hepatic injuries. Two had multiple liver lacerations oversewn; in the others temporary perihepatic packing was life saving[21–23]. It is important that the packs are positioned correctly around the injured lobes of the liver in a manner that will achieve tamponade (*Fig. 2*). This involves full mobilization of the liver by dividing its ligamentous attachments and the placement of large laparotomy packs around the superior and lateral aspects of each liver lobe. Following stabilization in intensive care these patients later underwent definitive surgery.

Perihepatic packing has been reported to be particularly useful for vena caval injury[24]. Experimentally, it has been shown that caval injuries can heal spontaneously without suture repair, which clearly has implications for the use of packing[25]. Drainage was not employed primarily in any of the present patients as it may impede the tamponade achieved by perihepatic packing. Packs, ideally, should be left *in situ* for 24–48 h, assuming initial bleeding has been controlled and the child is stable[21–23]. Removal within 48 h is recommended to obviate sepsis and expedite definitive surgery under controlled conditions[23].

Coexistent injuries caused the mortality in this study. The two deaths were due to severe head and neck trauma, and were considered unavoidable. These findings are consistent with previously published series on hepatic trauma from adult and paediatric centres[3,4,7–9,26]. No complications such as missed visceral injury, haemobilia, liver abscess or delayed haemorrhage were encountered in patients managed conservatively[4,27–29]. Caution is required when a policy of non-operative therapy is instituted. Repeated clinical examination, complemented by serial radiology (plain film, CT or ultrasonography) and laboratory studies, is useful for monitoring these injuries.

This evolving experience confirms that liver trauma in selected children can successfully be managed without operation in a paediatric surgical centre with an organized trauma system. When there is a major life-threatening hepatic injury, the use of temporary perihepatic packs and delayed operation is effective and safe, rather than heroic attempts at definitive surgery. Coexistent injury, particularly head and neck trauma, is a significant cause of mortality in children who sustain blunt hepatic trauma. Many of these deaths are unfortunately not preventable.

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Short note

Bilateral laparoscopic adrenalectomy for Cushing's disease

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Bilateral adrenalectomy for pituitary-dependent hypercortisolism (Cushing's disease) is occasionally indicated when pituitary surgery has failed. Laparoscopic adrenalectomy has seldom been performed for this indication[1-4].

Patients and methods

Fifteen consecutive patients (12 women and three men) of median age 36 (range 22–58) years underwent attempted bilateral laparoscopic adrenalectomy for severe Cushing's disease. The preoperative physical status was classified as American Society of Anesthesiologists (ASA) grade I in one patient, ASA II in 13 and ASA III in the remaining patient. Patients were placed in a lateral decubitus position and left adrenalectomy was completed first. The patient was then turned right side up to remove the right adrenal gland. The ten patients in whom bilateral laparoscopic adrenalectomy was completed were compared retrospectively to a matched group of 12 patients treated by open surgery through a posterior approach just before the laparoscopic experience. Postoperative requirement for opiate analgesia was compared between the groups.

Results

Bilateral laparoscopic adrenalectomy was completed successfully in ten patients. Median operating time was 295 (range 195–360) min. In one patient, intraoperative haemorrhage necessitated transfusion of 2 units of blood. This patient developed a subphrenic abscess which required surgical drainage. The remaining nine patients had an uneventful postoperative recovery. Median hospital stay was 6 (range 4–8) days.

In five patients, after unilateral laparoscopic adrenalectomy, the remaining adrenal was removed by means of a transperitoneal or posterior approach. The reasons for conversion to open surgery were difficult dissection in four patients and severe hypercapnia in one.

In one case, technical difficulties resulted in rupture of the adrenal gland. All five patients had an uneventful postoperative course and were discharged after a median of 7 (range 5–9) days. A corticotrophin test performed 3 months after surgery revealed a positive cortisol response in the patient with a fragmented gland, as reported previously.

Comparison between results and outcome in patients who had successful surgery and matched surgical controls is summarized in *Table 1*.

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Table 1 Comparison of bilateral laparoscopic adrenalectomy and open bilateral adrenalectomy for Cushing's disease

	Laparoscopic ($n = 10$)	Open surgery ($n = 12$)
Age (years)*	36 (22–58)	37 (24–55)
Weight (kg)*	71 (62–93)	74 (61–98)
Sex ratio (F:M)	9:1	9:3
ASA status		
I	1	1
II	8	9
III	1	2
Duration of surgery (min)*	295 (195–360)	164 (130–245)
Blood transfusion (no. of patients)	1	3
Complications	1†	3‡
Death	0	0
Duration of postoperative opiate analgesia (days)*	4 (2–5)	7 (5–10)
Length of hospital stay (days)*	6 (4–8)	10 (8–18)

Values are median (range). †One subphrenic abcess requiring surgical drainage; ‡two chest infections and two wound infections in three patients. ASA, American Society of Anesthesiologists

Discussion

This initial experience of 15 patients illustrates the limits and advantages of bilateral laparoscopic adrenalectomy for Cushing's disease. The median operating time was longer than for open surgery. This was due to the need to change the patient's position. Even though laparoscopic adrenalectomy can be performed transperitoneally in a supine position or using a retroperitoneal approach[1,3,4], the authors and others[1] believe that the laparoscopic flank approach results in better exposure and easier dissection. Difficult dissection due to obesity and fragility of periadrenal tissue was the reason for conversion to open surgery after left adrenalectomy in four patients. The operating time and conversion rate should reduce with increasing experience.

This preliminary report suggests that the requirement for postoperative analgesia and the duration of hospital stay is reduced after successful laparoscopic adrenalectomy. There may also be advantages in reducing postoperative complications as a result of the less traumatic approach.

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Surgical workshop

Video-assisted distal carotid artery surgery

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Surgery in the distal carotid sheath is challenging because access is difficult and injury to the seventh, ninth, tenth and twelfth cranial nerves may result in considerable morbidity. A number of techniques have been described to facilitate exposure of the upper reaches of the internal carotid artery or para-arterial structures, including division of the digastric muscle, resection of the styloid process, temporomandibular joint subluxation, mandibular osteotomy, partial mastoidectomy and opening of the bony carotid canal[1–4]. In this report the use of a laparoscope to visualize carotid dissection at the base of the skull through a standard neck incision is described.

Surgical technique

A 56-year-old woman with a history of hypertension and persistent tachycardia was found to have a markedly raised concentration of urinary free catecholamines in association with a lump in the right side of the neck. Investigations revealed a neuroectodermal tumour within the carotid sheath, involving the vagus nerve and extending into the jugular foramen (*Fig. 1*).

Through a routine exposure the proximal tumour was dissected from the carotid bifurcation. A 10-mm diameter laparoscope and camera (Dyonics; Smith and Nephew, Cambridge, UK) attached to a light source and video monitor was then inserted into the open wound to visualize the distal internal carotid artery, the ninth and twelfth nerves, the tumour mass entering the base of the skull and the tips of the dissecting instruments working beyond the upper margin of the wound (*Fig. 2*), allowing safe completion of the excision. Histological and biochemical assessment demonstrated complete resection of the phaeochromocytoma and the patient made a good recovery. Initial difficulties with swallowing resolved spontaneously.

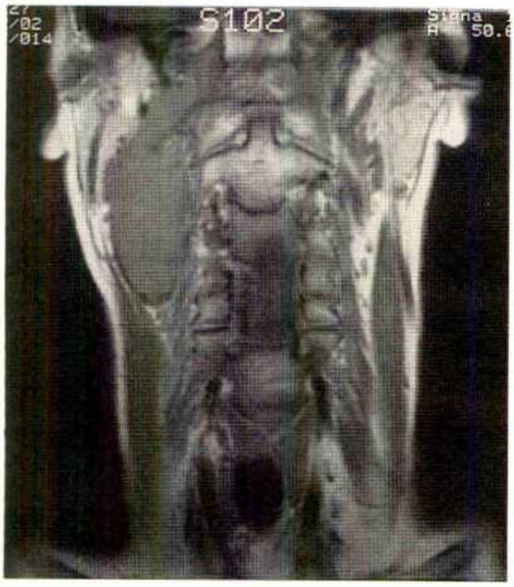

Fig. 1 Sagittal magnetic resonance image showing a large right-sided mass in the neck with a dumbell-shaped extension into the bony jugular foramen on the base of the skull

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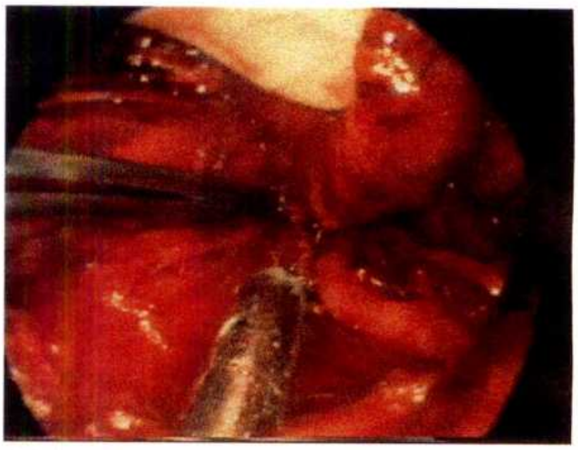

Fig. 2 View of the proximal extent of the tumour, internal carotid artery and glossopharyngeal nerve as seen through the laparoscope during dissection

Discussion

Adequate visualization of the contents of the carotid sheath is essential during surgery on the distal internal carotid artery and associated structures. The use of a laparoscope to guide distal dissection allowed successful resection of a malignant tumour extending into the jugular foramen through a standard incision. The method provides clear, magnified images of the operation site and requires little expertise in addition to that required for conventional surgery on the distal carotid artery, other than the ability to operate while observing the procedure on a nearby monitor.

Video assistance may be valuable during difficult carotid surgery, such as high aneurysm repair, to allow precise dissection of the artery distal to the lesion, preservation of the cranial nerves (particularly the glossopharyngeal) and clamp placement near the skull base.

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Surgical workshop

Partial portal arterialization for dearterialized liver after hepatectomy

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Following a portacaval shunt, portal arterialization has been used to avoid a decrease in hepatic blood flow[1,2]. In 1992 Iseki and colleagues[3] described partial portal arterialization to raise the portal oxygen pressure for the prevention of liver necrosis due to obstruction of the hepatic artery after extended pancreatobiliary surgery. The authors carried out partial portal arterialization using the ileocolic artery and vein to prevent postoperative hepatic failure resulting from obstruction of the hepatic artery after hepatectomy. The technique of and indications for partial portal arterialization following hepatectomy are reported.

Surgical technique

After major hepatectomy, the ileocaecal region is mobilized. The ileocolic artery and vein are exposed at the proximal portion of the marginal vessels and are anastomosed with a side-to-side continuous suture using 7/0 polypropylene under a loupe. This technique is simple and easy.

This method was applied for three major hepatectomies. The reasons for poor blood flow of the hepatic artery to the remnant liver were failure of the arterial reconstruction, insufficient collateral formation after obstruction of the proper hepatic artery, and inability to reconstruct the hepatic artery.

The postoperative course was uneventful in the first and the third cases; the second patient died from pulmonary oedema and the effect of the method was not evaluated. In the first patient, postoperative angiography on day 43 after operation demonstrated obstruction of the anastomosis. In the third patient, postoperative angiography on the 29th postoperative day showed a patent anastomosis and no reflux to the splenic vein (*Fig. 1*). Upper gastrointestinal endoscopy indicated no oesophageal varices at 6 months after surgery. Haemolysis and ascites due to portal hypertension did not occur in patients 1 and 3.

Discussion

As the hepatic artery has many collateral vessels, its obstruction is said merely to cause infarction of the liver. However, when the collateral vessels are blocked off as a result of lymphadenectomy of the hepatoduodenal ligament and mobilization around the liver, postoperative complications such as hepatic failure and anastomotic leakage occur frequently owing to obstruction of the hepatic artery[3].

Portal arterialization may prevent liver damage following portacaval shunt for portal hypertension in patients with cirrhosis[1,2]. This is a total portal arterialization to maintain the blood flow of the cirrhotic liver after end-to-side portacaval anastomosis. In contrast, the portal arterialization reported here is a partial portal arterialization to prevent hepatic failure after hepatectomy accompanied by obstruction of the artery of the remnant liver.

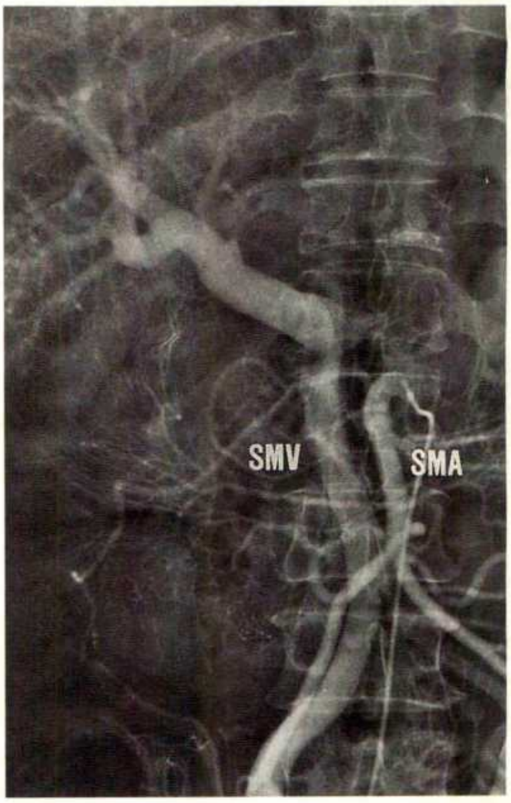

Fig. 1 Angiography via the superior mesenteric artery (SMA) on the 29th postoperative day (the third patient). Early filling of the superior mesenteric vein (SMV) indicates that the anastomosis between the ileocolic artery and vein is patent

Partial portal arterialization by side-to-side anastomosis of the ileocolic artery and vein is recommended as an easy and useful measure to prevent hepatic failure for dearterialized liver after hepatectomy. As the ileocolic artery and vein have a narrow lumen, portal hypertension due to the anastomosis does not seem to occur, in this small experience. However, for the prevention and treatment of portal hypertension resulting from the arteriovenous anastomosis, transcatheter embolization of the ileocolic artery would be easy and effective.

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Patterns of lymphatic spread of carcinoma of the ampulla of Vater

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Background The pattern of lymphatic spread of ampullary cancer is poorly documented. This pattern was clarified in order to define the rational extent of radical lymphadenectomy.

Method Thirty-nine consecutive patients who underwent pancreaticoduodenectomy with radical lymphadenectomy were included in the study. A total of 1447 lymph nodes dissected from the resected specimens was examined to detect the presence of metastatic foci.

Results Twenty-one of the 39 patients had a total of 97 positive nodes. The sites of nodal involvement were the posterior pancreaticoduodenal (20 of 21 patients), inferior pancreaticoduodenal artery (IPDA; 12 of 21), anterior pancreaticoduodenal (three of 21), trunk of the superior mesenteric artery (three of 20), pericholedochal (three of 21), retroportal (two of 21), and para-aortic (three of five) regions. No metastases were found in the hepatic artery, cystic duct, perigastric, right coeliac, middle colic artery or right caval node groups.

Conclusion Ampullary cancer mainly spreads to the posterior pancreaticoduodenal node group, then to the IPDA node group, and finally to the para-aortic area. The rational extent of radical lymphadenectomy should include the pancreaticoduodenal, superior mesenteric, pericholedochal, retroportal and para-aortic nodes.

The goal of radical surgery for cancer is to achieve permanent locoregional control. Because good local control can be achieved in ampullary carcinoma, knowledge of the pattern of regional lymphatic spread is mandatory to reach this treatment goal. Although there are several studies regarding lymphatic spread of pancreatic cancer[1–5], only a few studies have been reported concerning the pattern of lymphatic spread of ampullary cancer[1,6]. Earlier studies[1,4,6] have demonstrated that ampullary cancer most frequently involves the posterior pancreaticoduodenal nodes which are the 'first echelon' nodes of the periampullary region. However, further definition of the route of lymphatic spread is lacking. Although several authors have recommended radical lymphadenectomy for this disease[6–12], there have been no reports that delineate the rational extent of radical lymphadenectomy.

The aims of this study were to clarify the topographical distribution of lymph nodes around the head of the pancreas and to delineate the pattern of lymphatic spread of ampullary cancer by examining radical pancreaticoduodenectomy specimens. The practical goal was to define the rational extent of radical lymphadenectomy for this disease.

Patients and methods

From 1977 to 1994, 40 consecutive patients with ampullary carcinoma underwent resection in this department and its affiliated institutions. There were 38 adenocarcinomas and two adenosquamous carcinomas. One patient had a local resection alone and was excluded. Thirty-six patients had a classic Whipple operation with radical lymphadenectomy. Since October 1991, three patients underwent a pylorus-preserving pancreaticoduodenectomy with radical lymphadenectomy. The 39 patients who underwent radical lymphadenectomy were selected as the study subjects. There were 15 women and 24 men whose ages ranged from 45 to 82 (mean 60·9) years. No operative deaths occurred in this series.

Classification of lymph node groups

In this study, the lymph node groups around the head of the pancreas were classified and named as illustrated in *Fig. 1*. This nomenclature is a refinement of previously proposed systems[1,4,13–18]. Each lymph node group was designated as follows: hepatic artery, nodes along the proper or common hepatic artery; pericholedochal, nodes along the common bile duct; cystic duct, node(s) along the cystic duct,; anterior pancreaticoduodenal, nodes on the anterior aspect of the head of the pancreas usually located along the anterior pancreaticoduodenal arterial arcade; posterior pancreaticoduodenal, nodes on the posterior aspect of the head of the pancreas usually located along the posterior pancreaticoduodenal arterial arcade; perigastric, nodes around the stomach (including the infrapyloric nodes); retroportal, nodes posterior to the portal vein; right coeliac, nodes right to the coeliac axis; and superior mesenteric, nodes around the superior mesenteric artery (SMA).

The superior mesenteric nodes were subdivided into three groups: nodes around the trunk of the SMA; inferior pancreaticoduodenal artery (IPDA) nodes, around the IPDA (including those around the trunk of the first jejunal artery); and middle colic artery (MCA) nodes, around the origin of the MCA. The IPDA and first jejunal artery may or may not originate from a common stem[19–21]. *Fig. 2* illustrates two main variations of the arteries and the distribution of the IPDA nodes around them.

The para-aortic lymph nodes were subdivided into three groups by their relationships with the centre lines of the aorta and the vena cava, designated as right caval, interaorticocaval and left aortic.

Lymphadenectomy procedure

Regional lymph nodes were dissected *en bloc* together with the resected viscera. The degree of superior mesenteric node dissection varied considerably depending on the individual surgeon's preference: about half of the patients underwent a dissection of the right half of the trunk of the SMA node group

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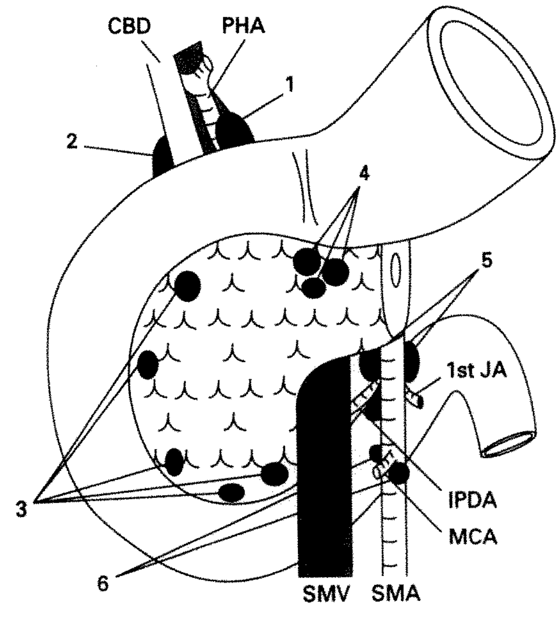
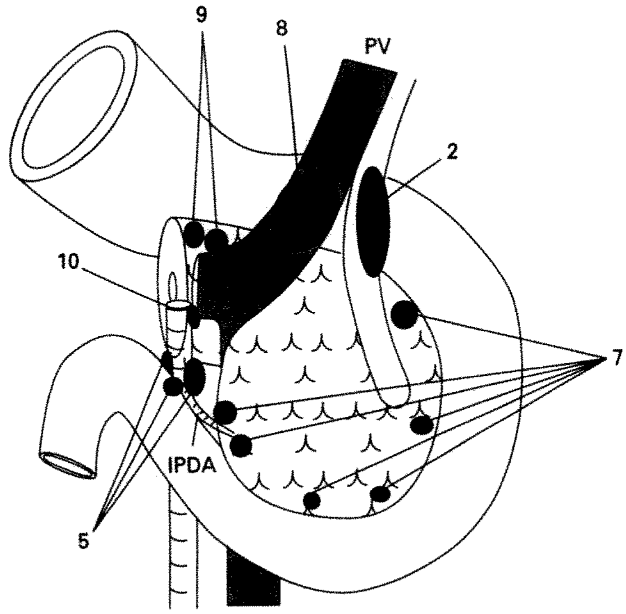


a Anterior



b Posterior

Fig. 1 Classification of lymph nodes around the head of the pancreas. **a** anterior aspect and **b** posterior aspect. Lymph node groups are: 1, hepatic artery; 2, pericholedochal; 3, anterior pancreaticoduodenal; 4, infrapyloric (included in perigastric nodes); 5, inferior pancreaticoduodenal artery (IPDA); 6, middle colic artery (MCA); 7, posterior pancreaticoduodenal; 8, retroportal; 9, right coeliac; 10, trunk of the superior mesenteric artery (SMA). CBD, common bile duct; PHA, proper hepatic artery; 1st JA, first jejunal artery; SMV, superior mesenteric vein; PV, portal vein

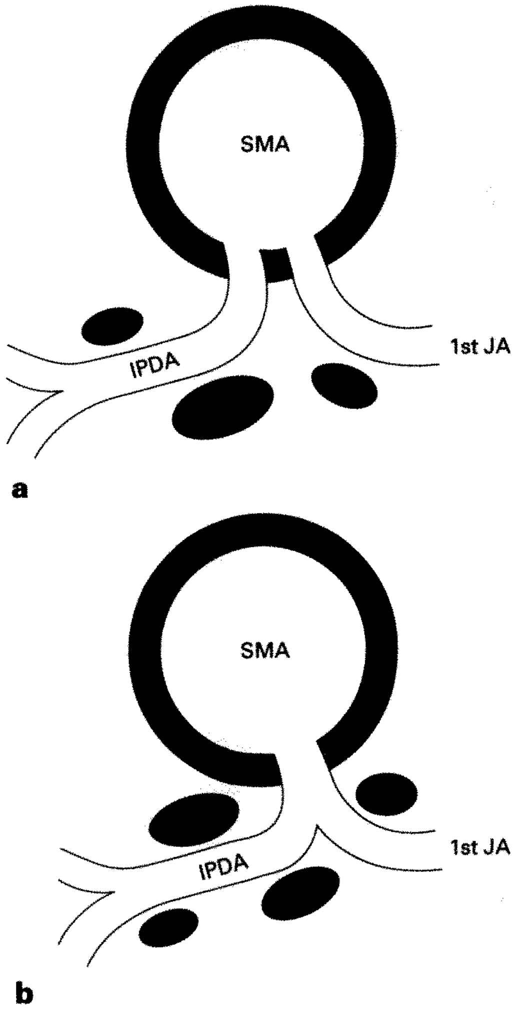


Fig. 2 Distribution of the inferior pancreaticoduodenal artery (IPDA) nodes. Solid ellipses represent individual lymph nodes. The figures, which represent cross-sections of the superior mesenteric artery (SMA), show two main variations in its arterial branching: either the IPDA and first jejunal artery (1st JA) originate separately (**a**) or both arteries originate from a common stem (**b**). Division of the trunk of the IPDA or the common stem is required to dissect the IPDA nodes thoroughly

and the IPDA node group, with division of either the IPDA or the common stem of the IPDA and first jejunal artery (*Fig. 2*). The right lateral wall of the SMA was exposed at the end of the dissection. The other patients underwent a less aggressive superior mesenteric node dissection.

The superior mesenteric nodes to the left of the SMA, the superior mesenteric plexus[22] and left coeliac ganglion[22] were not resected in any patient, because ampullary carcinoma seldom involves these tissues[11].

In June 1989, dissection of the para-aortic lymph nodes in patients with suspected nodal metastasis (clinical N_1 disease[15]) was started. Eight patients have undergone this procedure. Para-aortic lymph nodes cephalad to the origin of the inferior mesenteric artery, excluding the left aortic nodes cephalad to the left renal vein, were resected in this procedure.

Histological examination

Lymph nodes were dissected out from the *en bloc* specimens after surgery and were separated into each node group. A single representative section of each lymph node was examined histologically to detect the presence of metastatic foci. The extent of the primary tumour was determined on multiple sections[23].

Statistical analysis

The Mann–Whitney U test and Fisher's exact test were used to compare data. A difference was regarded as statistically significant if the P value was less than 0·01.

Results

Distribution of lymph nodes around the head of the pancreas

A total of 1447 lymph nodes was dissected from specimens from 39 patients. The number of lymph nodes per patient ranged from 13 to 69 (median 32; mean 37·1).

Distribution of positive nodes

Twenty-one of the 39 patients had a total of 97 positive nodes. The number of positive nodes per patient ranged from 1 to 23 (median 2; mean 4·6). The topographic distribution of positive nodes is shown in *Table 1*. In nine patients with disease limited to only one lymph node group, the positive nodes were found in the posterior pancreaticoduodenal group in all but one patient. In 12 patients with metastasis to multiple lymph node groups, the superior mesenteric nodes were positive in all but one patient.

Among those with nodal disease, there were nine patients with pancreatic invasion. All of the patients with pancreatic invasion had involvement of multiple lymph node group with metastases to the superior mesenteric node group. The patients with pancreatic invasion had more positive nodes ($P = 0\cdot0004$), a higher incidence of metastasis to the superior mesenteric nodes ($P = 0\cdot0011$), more multiple node group involvement ($P = 0\cdot0011$) and three or more node group involvement ($P = 0\cdot0003$) than those without pancreatic invasion.

Of the three groups of superior mesenteric nodes, the IPDA node group was involved more frequently than the other groups ($P = 0\cdot0088$). The MCA nodes were not involved in any case ($n = 6$).

Three patients with pancreatic invasion had positive para-aortic nodes in the interaortic ocaval and left aortic node groups. The right caval nodes were not involved.

Table 1 Nodal status in 21 patients with lymph node metastasis

	No. of patients	
Node group	Positive nodes	Node group examined*
Posterior pancreaticoduodenal	20	21
Anterior pancreaticoduodenal	3	21
Inferior pancreaticoduodenal artery	12	21
Trunk of the superior mesenteric artery	3	20
Middle colic artery	0	6
Pericholedochal	3	21
Retroportal	2	21
Hepatic artery	0	20
Perigastric†	0	18
Cystic duct	0	21
Right coeliac	0	21
Interaorticocaval	3	5
Left aortic	2	5
Right caval	0	5

*Indicates number of patients in whom the node group was dissected and examined. †Includes infrapyloric nodes

Outcome after surgery

Eight of the 14 patients with involvement of one or two lymph node groups, including three patients with positive superior mesenteric nodes, survived longer than 5 years, although three of the eight survivors died from disease at 132 months, 64 months and 61 months after resection.

Six of the seven patients with involvement of three or more lymph node groups died from disease within 28 months after resection. The remaining patient was alive with no evidence of disease 12 months after resection.

Route of lymphatic spread

The route of lymphatic spread of ampullary cancer, was derived from analysis of patients with involvement of one, two or more node groups (*Fig. 3*). The disease appears mainly to spread to the posterior pancreaticoduodenal node group, then to the IPDA node group, and finally to the para-aortic nodes.

Discussion

The nomenclature of the lymph node groups around the head of the pancreas is not standardized. Although Rouvière[13], Evans and Ochsner[14] and Cubilla *et al.*[1] have proposed their own excellent classifications, they described poorly the lymph node groups located behind the pancreas or around the SMA. Even in the tumour node metastasis staging system[15] and the *Nomina Anatomica*[16], the specific location of each node group is not illustrated. The Japanese classifications[17,18], both written in Japanese, are too complicated to use in clinical practice. The classification system outlined in this report seems to be useful for documenting nodal spread in the head of the pancreas area.

Pattern of lymphatic spread

Ampullary cancer most frequently spreads to the posterior pancreaticoduodenal node group. Similar results have been reported elsewhere[1,4,6,11]. Thus, the posterior pancreaticoduodenal node group is the most important of the first echelon node groups.

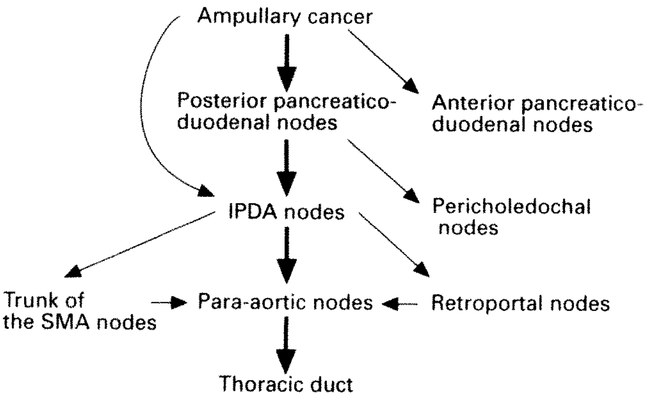


Fig. 3 Diagrammatic representation of routes of lymphatic spread of ampullary tumour. Arrows indicate individual routes, with thick arrows denoting the main route via the posterior pancreaticoduodenal and inferior pancreaticoduodenal artery (IPDA) node groups. SMA, superior mesenteric artery

Positive superior mesenteric nodes were found in 12 patients, of whom 11 also had positive posterior pancreaticoduodenal nodes and the other patient had only a single positive superior mesenteric node. Metastasis to the superior mesenteric nodes appears to follow involvement of the posterior pancreaticoduodenal nodes, while it may occasionally occur primarily. Of the superior mesenteric nodes, the IPDA node group was most frequently involved, indicating that this is a key distant node group.

Ampullary cancer usually has a limited extent of nodal disease[1,4,6,11], while pancreatic cancer often shows extensive nodal involvement[1–4,11]. In this series, pancreatic involvement was closely related to extensive nodal involvement. Thus, ampullary cancer invading the pancreatic parenchyma may act more like pancreatic cancer with regard to nodal spread. This may explain why ampullary cancer with pancreatic invasion has such a poor prognosis[6,23,24].

Despite no previous reports identifying para-aortic nodal involvement in resectable ampullary cancer[11], three patients in this series had para-aortic nodal involvement. This suggests that para-aortic nodal involvement may not be rare in patients with extensive nodal disease.

Rational extent of radical lymphadenectomy

In this series, metastases never involved the hepatic artery, perigastric, cystic, right coeliac, MCA and right caval node groups. Based on the distribution of positive nodes, the rational extent of radical lymphadenectomy for this disease includes the posterior pancreaticoduodenal, IPDA, anterior pancreaticoduodenal, trunk of the SMA (only right half), pericholedochal and retroportal node groups. In addition, the interaorticocaval and left aortic node groups may be included in the case of more advanced disease.

Although the prognosis of extensive nodal involvement was dismal, eight patients with nodal disease survived 5 years in this series. The application of radical lymphadenectomy appears to be justified for this disease.

Although long-term survivors with positive superior mesenteric nodes have been only rarely reported[6,25], three patients with positive superior mesenteric nodes survived 5 years in this series. Superior mesenteric node dissection with division of the IPDA may be efficacious for some patients.

Recurrence in the para-aortic nodes is a cause of failure after pancreaticoduodenectomy for ampullary cancer[24,26]. Para-aortic nodal dissection may enhance locoregional control in advanced tumours. Of the three patients with positive para-aortic nodes in this series, a potentially curative resection was feasible in one patient, who has survived for 1 year without evidence of disease at the time of writing. Another patient survived for 27 months in spite of far-advanced disease with residual tumour. Thus, the significance of para-aortic lymphadenectomy remains unclear.

Limitations

The main limitations of this study include variability in the degree of superior mesenteric node dissection and the small number of patients. Despite these limitations, the pattern of lymphatic spread has been defined more clearly than by earlier authors.

In conclusion, ampullary cancer first spreads to the pancreaticoduodenal and IPDA node groups and then to other peripancreatic node groups including the para-aortic nodes. The rational extent of radical lymphadenectomy for this disease includes the pancreaticoduodenal, superior mesenteric, pericholedochal, retroportal and para-aortic nodes.

Acknowledgements

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Oral erythromycin improves gastrointestinal motility and transit after subtotal but not total gastrectomy for cancer

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Background Erythromycin has been shown to be a powerful prokinetic of the gastrointestinal tract. Little is known about its value to improve motility and transit in gastrectomized patients.

Methods Thirteen disease-free patients subjected to subtotal gastrectomy and 11 subjected to total gastrectomy for gastric cancer entered the study. Gastrointestinal transit of a standard ^{99m}Tc-labelled meal and fasting motility were studied before and after oral erythromycin.

Results In patients who had subtotal gastrectomy mean(s.d.) gastric half-emptying time was 42(14) min before and 26(11) min after erythromycin ($P = 0·011$). Before erythromycin prolonged rhythmical contractions (3 per min) were recorded in eight patients, sporadic non-organized contractions in two and prolonged bursts of waves in one. After erythromycin, clustered waves resembling a migrating motor complex (MMC) appeared in eight patients, while rhythmic motor activity was unchanged in three. In patients who had total gastrectomy jejunal half-emptying time was 39(18) min before and 45(12) min after erythromycin. In eight patients, frequent MMCs were recorded, peristaltic in four, synchronous in one, antiperistaltic in two, with clusters of non-propagated waves in one. After erythromycin, longer peristaltic MMCs were recorded in three, antiperistaltic MMCs persisted in two, synchronous in one and clusters of non-propagated waves in two.

Conclusion Oral erythromycin improves gastrointestinal transit and motility after subtotal gastrectomy. The findings after total gastrectomy are controversial.

The past ten years have seen an increased interest in the effects of erythromycin and its derivatives on the motility of the gastrointestinal tract, both experimentally and clinically[1,2], and the emergence of new, powerful prokinetic agents. The availability of such drugs is of major clinical relevance in many postoperative and acquired disturbances of gastrointestinal motility and transit, where conventional treatment may be ineffective.

Erythromycin and other 14-membered erythronolide derivatives have been shown to improve motility and transit when given intravenously or by mouth to patients with diabetic gastroparesis[3], intestinal pseudo-obstruction[4,5], scleroderma[6] and in surgically-induced digestive problems following duodenopancreatectomy[7] or oesophagectomy[8,9]. The mechanisms by which erythromycin stimulates gastrointestinal smooth muscles have not been fully elucidated, although there is evidence that it acts on the motilin receptor in the gut[10] and the integrity of the cholinergic pathway[11] seems to be required. Calcium-mediated mechanisms[12], nitric oxide, and vasoactive intestinal polypeptide (VIP)[13] also appear to play a role. Postoperative sequelae of some surgical procedures, such as oesophagectomy, total gastrectomy and radical subtotal gastrectomy, are the result of cholinergic denervation of the viscera after division of the vagus. Vagal denervation may only be part of the problem, as truncal vagotomy of otherwise intact viscera results in moderate postoperative complications like diarrhoea and gastric atony[14], whereas severe impairment of gastrointestinal motility and transit occur only after gastric resection or total removal of the stomach with various intestinal reconstruction procedures. These transit problems may be related to partial or total intestinal obstruction[15]. Patients who have undergone extensive resection show profound alterations of gastrointestinal motility patterns with clinical symptoms of nausea and abdominal pain, known as the Roux stasis syndrome[16,17]. Prokinetic drugs such as metoclopramide and domperidone are often prescribed to alleviate symptoms in such patients but they are not always effective.

The aim of this paper was to study the effects of oral erythromycin administration on gastrointestinal transit and motility in patients after total or subtotal gastrectomy for cancer, and to assess which patients derived the most benefit from this treatment.

Patients and methods

Patients

The study was carried out over a 12-month period during which 24 patients (11 men) underwent surgery for gastric cancer ($n = 23$) or gastric leiomyoma ($n = 1$). The ages ranged between 36 and 78 (median 64) years. Thirteen patients underwent subtotal gastrectomy with a Hofmeister–Finsterer reconstruction and 11 had total gastrectomy with a stapled Roux–Orr reconstruction[18]. Median follow-up was 20 (range 6–240) months.

The postoperative evaluation of disease stage in the 23 patients with cancer was as follows: $T_1 N_0 M_0$ ($n = 4$), $T_2 N_0 M_0$ ($n = 4$), $T_3 N_0 M_0$ ($n = 6$), $T_2 N_1 M_0$ ($n = 3$), $T_3 N_1 M_0$ ($n = 3$), $T_3 N_2 M_0$ ($n = 2$), $T_3 N_3 M_0$ ($n = 1$).

Patients with recurrence of disease, evidence of metastases or anastomotic stricture, detected by endoscopy, computed

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tomography, abdominal ultrasonography and tumour markers, were excluded from the study.

Seven of the 11 patients who had had a total gastrectomy and six of the 13 who had undergone subtotal gastrectomy complained of early fullness during a meal, sometimes accompanied by abdominal pain or nausea. Three patients in the former group and four in the latter group took domperidone or metoclopramide with inconsistent relief. All had normal bowel habit except four who remained constipated as before surgery, and one patient who suffered diarrhoea for 6 months following total gastrectomy and a prolonged period of total parenteral nutrition.

All patients gave oral informed consent to the study after receiving full information about the aims and protocol.

Methods

Clinical and nutritional problems were documented using a detailed questionnaire on quantitative and qualitative changes in dietary habit, postgastrectomy symptoms, and the use of prokinetic drugs. All drugs likely to have an action on intestinal motility were withdrawn at least 3 days before the study.

Gastrointestinal transit. Transit was investigated using a standard test meal[19] consisting of one scrambled egg labelled with 100 MBq ^{99m}Tc-labelled tin colloid together with two slices of toast and 300 ml tap water, and ingested within 10 min. The patient was then asked to lie down in a supine position under a broad-field scintiscanner.

The scintiscanner was placed parallel with and close to the patient's abdominal wall. Using a gamma camera computer system (Starcam 4000; General Electric, Milwaukee, Wisconsin, USA), dynamic acquisition of images (140 Kev ± 20 per cent photopeak, LEHR collimator, 128 × 128 matrix) was begun immediately after isotope ingestion at the rate of 1 image per min for 60 min, with a total of 60 sequential images. The region of interest (ROI) was drawn manually on the first image around the radioactive area corresponding to the remnant stomach in patients who had undergone subtotal gastrectomy or to the jejunal loop in those who had had a total gastrectomy. After correction for decay, half-emptying time, defined as the period needed for the radioactivity in the ROI to fall to 50 per cent of the starting value, and the percentage of remaining activity in the ROI after 60 min (residual radioactivity) were calculated for each patient. The occurrence of any reflux episode (gastro-oesophageal or jejunogastric) was also recorded.

The isotope transit study was carried out under basal conditions, before drug administration, and repeated after 3 days of erythromycin treatment (500 mg erythromycin (Abbott, SpA, Campoverde di Aprilia (Latina), Italy) orally three times a day). The medication was taken just before the study

Gastrointestinal manometry. Manometry was performed in the morning, after an overnight fast 1 week after erythromycin had been discontinued. An extra-thin silicone-sheathed probe (Gaeltec, Isle of Skye, UK), 3 mm in diameter, with three microtransducers 5 cm apart with a 90° phase angle was inserted through the nose into the gastric remnant, or into the jejunal limb in the case of total gastrectomy. The position of the probe was checked by fluoroscopy. The probe was then connected to a digital recorder dedicated to manometry, and intraluminal pressure was recorded for 150 min. Pressure traces were displaced on a screen throughout the study After a basal period of 60 min, the patient was given a single dose of 500 mg erythromycin ethyl succinate by mouth, and gastric motility was recorded for a further 90 min.

The recorded pressure traces were analysed using dedicated software (Phoenix, Dingwall, UK) to identify the motility pattern before and after erythromycin administration, particularly focusing on the occurrence and characteristics (amplitude of contractions, propagation, duration) of interdigestive migrating motor complexes (MMCs).

Statistical analysis

Half-emptying times and percentages of residual radioactivity before and after erythromycin were compared using the Wilcoxon signed rank test for paired data.

Results

Subtotal gastrectomy

Of 13 patients who underwent subtotal gastrectomy, two declined to have manometry and to repeat the transit study with erythromycin. Emptying of the gastric remnant was significantly improved by erythromycin. Gastric half-emptying time significantly decreased from a mean(s.d.) basal value of 42(14) min to 26(11) min ($P = 0{\cdot}011$) after erythromycin. There was a statistically significant difference in the percentage of residual radioactivity after

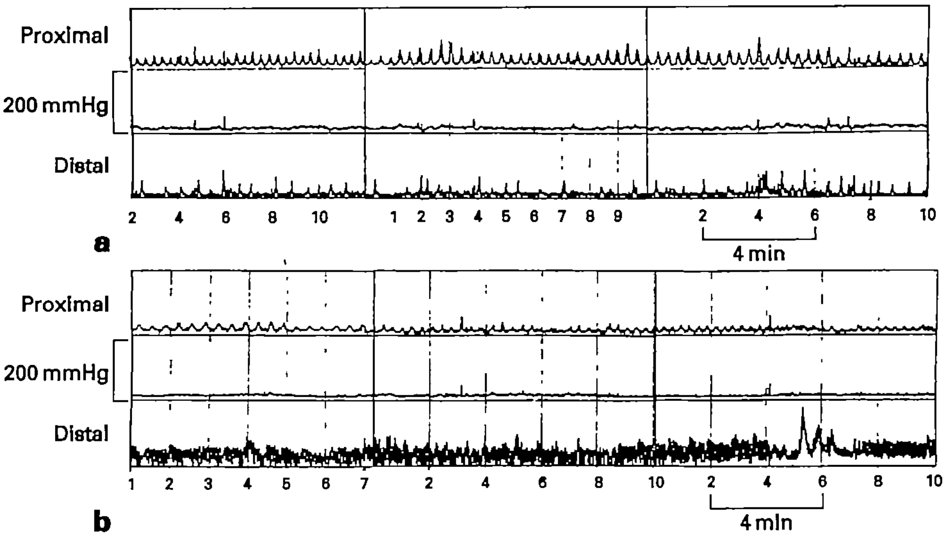

Fig. 1 Gastric manometry *a* before and *b* after erythromycin showing rhythmic slow waves in the fundus and intense contractile activity in the distal gastric remnant after oral erythromycin in a patient with subtotal gastrectomy

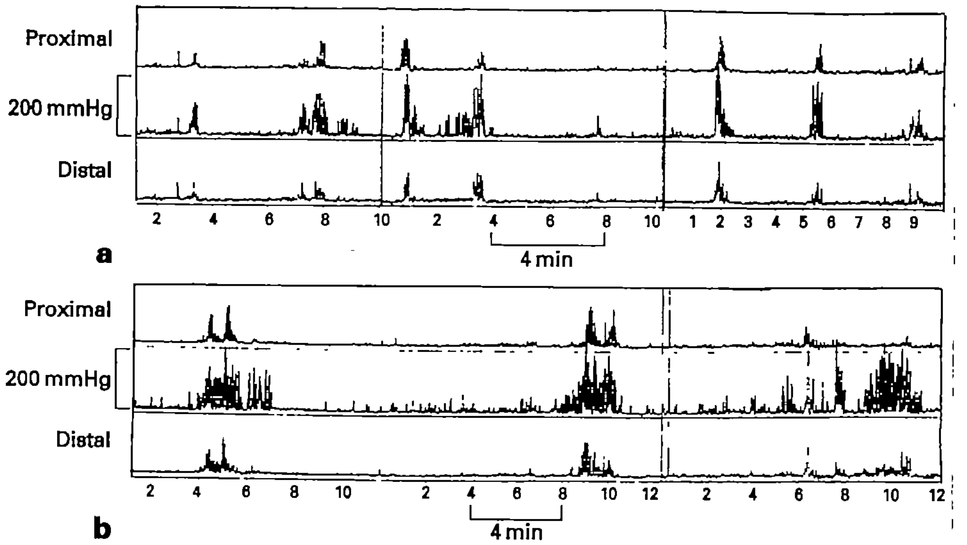

Fig. 2 a Synchronous migrating motor complexes (MMCs) in a patient after total gastrectomy. b After oral erythromycin the MMCs become longer and less frequent but remain synchronous

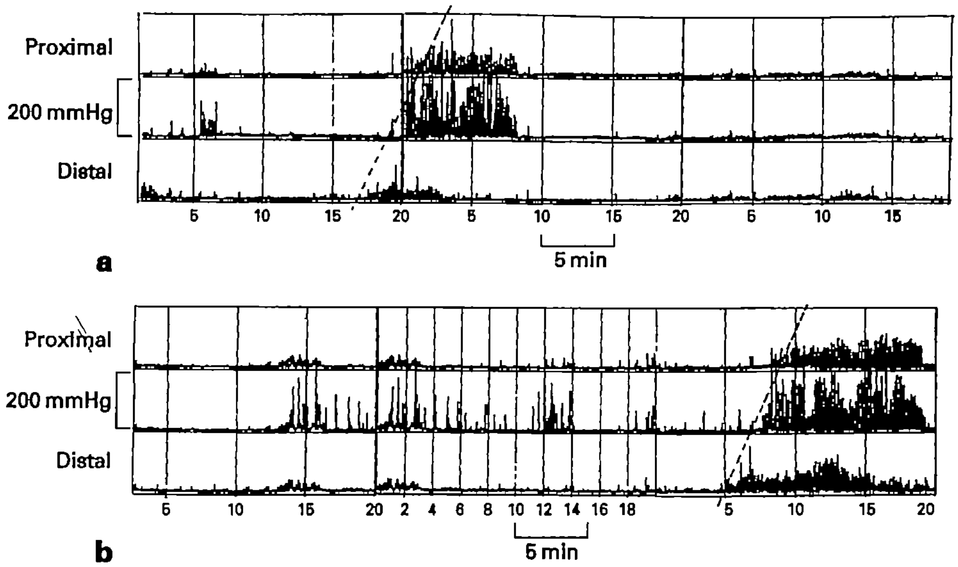

Fig. 3 Gastric manometry a before and b after erythromycin, showing migrating motor complex persisting unmodified after oral erythromycin in a patient after total gastrectomy

erythromycin (basal 36 per cent, erythromycin 11 per cent, $P = 0{\cdot}013$). Transit time improved in all patients, except one in whom asymptomatic jejunogastric reflux occurred during the study. Two other patients had jejunogastric reflux before erythromycin, but this was not seen after erythromycin. Three of the six patients with digestive problems reported improved digestion during erythromycin treatment.

Fasting basal manometry showed persistence of gastric cyclic motor activity, characterized by rhythmic slow waves (3 per min) of low–medium amplitude in eight patients (*Fig. 1*). Two had sporadic non-organized low-amplitude contractions, and prolonged bursts of contractions were recorded in one. The effects of erythromycin occurred after a median latency of 40 min. The continuous contractions seen under basal conditions were replaced by bursts of clustered waves which sometimes mimicked an MMC. High-amplitude contractions were sometimes seen in the distal part of the gastric remnant, while cyclic slow waves persisted proximally (*Fig. 1*).

In three patients the motility pattern remained unchanged after erythromycin.

Total gastrectomy

Two of the 11 patients refused to undergo the transit study. Basal transit was measured in nine patients, but two refused to undergo repeat examination under erythromycin. Jejuno-oesophageal reflux was detected in two patients under basal conditions. After erythromycin, this was not seen in one patient, but did occur in the other and in a third patient. Digestive symptoms persisted in the seven symptomatic patients despite erythromycin treatment and one of them complained of abdominal pain and nausea early after erythromycin in the fasting state.

Jejunal half-emptying time was variable and was no different after erythromycin (mean(s.d.) 39(18), *versus* 45(12) min). Jejunal residual radioactivity was also not different after erythromycin (mean(s.d.) 41(32) *versus* 29(17) per cent, *P* not significant).

Jejunal manometry was performed in eight patients. During the basal period in seven patients, the three phases of the MMC were observed. Phase III was propagated in a caudal direction in four patients, in an oral direction in two patients and in one patient phase III occurred synchronously at the three sites of recording. The MMCs had a duration of 4–10 min, with a mean amplitude ranging from 30 to 200 (median 50) mmHg and were recorded every 12–70 (median 50) min. Clusters of non-propagated high-voltage contractions with no consistent pattern or relationship were recorded in the last patient.

Some 30–70 (median 40) min after erythromycin administration, increased motility was recorded in three patients. This was characterized by longer (up to 12 min) and more frequent MMCs (every 10–35 min) with the same amplitude. Synchronous MMCs persisted in one patient but with higher voltages and duration (*Fig. 2*), while the antiperistaltic MMCs did not change under erythromycin except for their length (10 *versus* 8 min, *Fig. 3*). The traces remained substantially unmodified in the other patients.

Discussion

This study demonstrates that motility and transit problems underlie the digestive disturbances experienced by patients who have undergone subtotal gastrectomy or total gastrectomy, and that oral erythromycin is able to bring about a marked improvement in these problems in patients with subtotal gastrectomy. In these patients erythromycin had a coordinated propulsive effect on the gastric remnant, causing an improvement in gastric half-emptying time and a reduction in the percentage residue by the end of the study. These effects were accompanied by the disappearance of jejunogastric reflux in two patients and subjective improvement of symptoms in three other patients. In patients who had had total gastrectomy there were no differences observed after administration of erythromycin.

The main differences between the two operative procedures are the saving of the vagal branches to the fundus and preservation of the gastric pacesetter area, and preservation of the normal sequence of viscera after subtotal gastrectomy with the Hofmeister–Finsterer reconstruction, unlike in total gastrectomy with the Roux–Orr reconstruction, where the main trunks of the vagus are resected and the distal jejunum is anastomosed to the oesophagus.

Although the effects of erythromycin are said to be more pronounced in the antropyloric region and duodenum, probably because of the higher density of motilin receptors, the fundus also seemed to be sensitive to its action: the 'cyclic' gastric rhythm of 3 contractions per min, observed in most patients in this study, was disrupted by bursts of contractions 30–40 min after erythromycin administration.

After total gastrectomy the results were conflicting, often with a worsening of pre-existing digestive dysmotility. Synchronous or antiperistaltic MMCs were not corrected by erythromycin, and in these patients half-emptying time was frequently delayed. Jejuno-oesophageal reflux persisted in one patient and was induced in another.

Interpretation of the data observed in patients with total gastrectomy is not easy. It may be that the afferent branch of the Roux limb, with a pacesetter of higher frequency than the jejunal limb anastomosed to the oesophagus, may interfere with motility distally, with the effect of causing antiperistaltic contractions in the jejunum and oesophageal reflux. The same mechanism may be involved in the Roux stasis syndrome, where impaired gastric emptying and jejunal transit cause early fullness, nausea and vomiting (*Fig. 4*). This situation would be exacerbated by erythromycin. If erythromycin increases motility in the duodenum more than in the ileum, where it can have an inhibitory effect, the motility disturbance may be amplified, resulting in increased transit time and more frequent episodes of oesophageal reflux.

The neural control of gastrointestinal motility involves the extrinsic autonomic nervous systems as well as a complex network of cholinergic and non-cholinergic, non-adrenergic nerves. Surgical interruption of the vagus may alter the coordination of this complex mechanism, and although truncal vagotomy does not have a dramatic effect on gastrointestinal motor patterns *per se*, it may cause severe dysmotility when associated with a surgical repositioning of intestinal loops. Transit and manometry in the unstimulated limb after total gastrectomy have been investigated[19–21]. These authors identified a high proportion of patients with motility and transit problems in the Roux limb. These motor abnormalities are similar to those reported with the Roux gastrojejunostomy[22], ascribed to inappropriate function of the jejunal pacemaker. The Roux limb may be said to be a functionally obstructed intestinal segment.

In the present study, the percentage of patients after total gastrectomy who showed MMC-like activity in the Roux limb was higher than in Bassotti's study[21], although the activity was uncoordinated in most of them and transit was impaired in four patients. These motor problems were not improved by erythromycin, which increased the

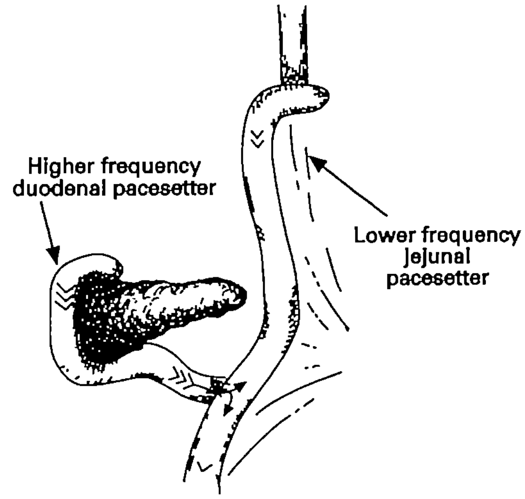
Higher frequency duodenal pacesetter
Lower frequency jejunal pacesetter

Fig. 4 Roux–Orr reconstruction after total gastrectomy for cancer showing the possible pace-setter sites

frequency of the pseudo-MMCs without improving propagation and delayed transit in most patients. Pharmacological correction of hypomotility in the Roux limb by erythromycin seems therefore inappropriate. New surgical procedures, such as the 'uncut Roux limb' proposed recently[23], might offer new solutions to the problem.

Although erythromycin acts at least in part via a cholinergic mechanism[11] it is evident from the results of this study that it can stimulate motility after truncal vagotomy. Erythromycin and its analogues are known to have a direct effect on intestinal smooth muscle *in vitro*, probably via a calcium-mediated mechanism[12]. *In vivo*, erythromycin improved antroduodenal coordination and facilitated gastric emptying. This class of molecules (motilides) may represent an important step forward in the search for an effective prokinetic agent in situations where traditional drugs like metoclopramide, domperidone or cisapride are ineffective, possibly because they require an intact nerve supply.

In conclusion, orally administered erythromycin, or its antibiotic-free derivatives now under investigation[24,25], may represent a valuable new prokinetic drug. Clinical benefit may be obtained in patients who have undergone subtotal gastrectomy, whereas its usefulness in patients after total gastrectomy is uncertain.

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Primary retroperitoneal germ cell tumours: excision via a thoracoabdominal extraperitoneal approach

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Background Primary retroperitoneal germ cell tumours usually present as a large abdominal mass in young men. The testes are normal on examination and ultrasonography but there are usually raised serum levels of human chorionic gonadotrophin and/or α-fetoprotein.

Methods Fourteen men (median age 33 years) with primary retroperitoneal germ cell tumours were treated by chemotherapy followed by surgical resection of the primary tumour and metastases via a thoracoabdominal extraperitoneal approach.

Results There was minimal morbidity. The survival rate was 13 of 14 and the disease-free survival rate was 11 of 14 after a median follow-up of 15 months.

Conclusion The thoracoabdominal extraperitoneal approach for the removal of retroperitoneal germ cell tumours and their metastases after chemotherapy improves tumour clearance, morbidity and recovery time compared with the transperitoneal anterior approach.

Primary retroperitoneal malignant tumours are rare and often present late when they have reached enormous dimensions. Approximately 10 per cent of malignant primary retroperitoneal tumours are extragonadal germ cell tumours (EGCTs)[1]. Malignant non-seminomatous germ cell tumours usually arise from the testis and are the most common solid tumour in males in the 20–35 years age group; the incidence of these tumours is increasing steadily[2]. Palpation of the testes is considered insensitive in excluding an occult primary tumour of the testis, but high-frequency ultrasonography may detect small tumours within the testis[3]. EGCT may also arise from the mediastinum, retroperitoneum, near the pineal gland and sacrococcygeal region. The retroperitoneum is the second commonest site, after the mediastinum, for the source of EGCT. Historically the results of primary surgical treatment of retroperitoneal EGCT have been disappointing, with an operative mortality rate of 21 of 39[1]. However, initial chemotherapy with a regimen containing vinblastine and bleomycin, followed by surgical removal of residual tumour masses, achieved a disease-free survival rate of eight in a series of 15 patients with primary retroperitoneal EGCT[4].

In a previous detailed analysis of 20 patients with extragonadal primaries[5], the survival rate in patients with mediastinal primary tumours was excellent, with eight of eight patients surviving in remission, but the rate for those with retroperitoneal primaries was seven of 12. A specific and intractable problem in the retroperitoneal primaries was duodenal involvement, which resulted in three of the five deaths.

A midline abdominal approach can be used for tumour excision in some patients, but if there is extension superior to the renal vessels it may be difficult to achieve complete excision. Supradiaphragmatic extension, either by direct invasion or metastatic spread to retrocrural lymph nodes or lung, necessitates thoracotomy as a separate procedure or via a thoracoabdominal approach. A further problem with the midline approach is paralytic ileus, which may develop after mobilization of the bowel to gain access to the retroperitoneum. For this reason the average inpatient stay after removal of retroperitoneal tumours via a midline approach is 10–14 days[6]. These problems led the authors to explore an alternative thoracoabdominal extraperitoneal approach for the removal of these tumours.

Patients and methods

A consecutive series of 14 men (median age 33 (range 24–64) years) presenting with a primary retroperitoneal EGCT mass were referred with a view to chemotherapy and/or surgical treatment. Initial presenting symptoms were abdominal mass, backache and weight loss in 13 patients and loss of ejaculation in one man. None of the patients gave a past history of cryptorchidism or hernia repair in childhood. Examination revealed an easily palpable abdominal mass in all cases and in one man enlarged cervical lymph nodes, which had previously been subjected to open biopsy In all cases both testes were examined clinically and by ultrasonography. In three patients unilateral testicular atrophy was apparent; however, thorough histological examination after excision of these testes revealed no evidence of tumour. In the other 11 cases clinical examination and ultrasonography revealed no clear evidence of tumour in either testis. Bilateral open testicular biopsies in three men showed no tumour or carcinoma *in situ*.

Serum levels of the tumour markers human chorionic gonadotrophin (hCG) and/or α-fetoprotein (AFP) were raised above the nomal range at presentation in 13 of the men

Histological confirmation of the diagnosis of retroperitoneal EGCT was made by computed tomography (CT)-guided needle biopsy in eight cases. In five cases the diagnosis was made from tissue taken at midline laparotomy at the referring hospital. One patient, aged 26 years, underwent cervical lymph node biopsy at the referring hospital where an erroneous diagnosis was made of anaplastic carcinoma; the patient had been referred for palliative care. However, review of the specimen and detection of raised levels of tumour markers led to a diagnosis of EGCT. In all 14 cases biopsy had revealed undifferentiated teratoma.

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Each patient was further assessed by pelvic, abdominal and thoracic CT, which revealed metastatic disease distant from the primary tumour in six cases.

Initially, each patient was treated with POMB-ACE (POMB = cisplatinum, vincristine, methotrexate and bleomycin; ACE = actinomycin D, cyclophosphamide and etoposide) chemotherapy every 10 days and the response was monitored by tumour marker assays[7]. Tumour marker concentrations were normal after chemotherapy in all cases. After completion of chemotherapy a further CT scan was performed. The location of metastatic disease after chemotherapy is shown in *Table 1*.

In the five patients who had previously undergone unsuccessful attempts to remove the tumour through midline incisions the residual disease was surrounding the aorta–inferior vena cava (IVC). In one case the referring surgeon had resected the aorta and replaced it with a straight Dacron (Du Pont, Stevenage, UK) graft which had been anastomosed proximally to the infrarenal aorta and surrounding residual tumour. A typical residual mass following chemotherapy is shown in *Fig. 1*.

Operative procedures

In all 14 cases, residual tumour was removed 4–6 weeks after chemotherapy via a thoracoabdominal extraperitoneal approach. A left-sided approach was used in nine cases and a right-sided approach in four; one patient, with extensive disease invading each psoas and with bilateral retrocrural lymph node involvement, underwent separate thoracoabdominal operations on each side with a 6-week interval between.

The patients were positioned in a supine semirotated position. The incision was made over the eighth rib through the costal cartilage to the lateral border of rectus abdominis and distally as a paramedian incision. The distal extent of the incision was dependent on the dimensions and location of the tumour and its metastatic component, and could be extended as far as the inguinal canal. The intercostal muscles and external costal periosteum were removed from the rib and the rib was excised by division proximal to its curvature. The parietal pleura was divided along the line of the rib, leading to deflation of the ipsilateral lung. The diaphragm was then divided along the line of the rib as far as, but not beyond, its tendinous portion. The peritoneum was reflected medially separating it from the diaphragm, abdominal wall musculature, quadratus lumborum and psoas major muscles.

Table 1 Metastatic disease present after chemotherapy

Site of metastatic disease	*n*
Retrocrural lymph nodes	3
Liver	2
Lung	4
Cervical lymph nodes	1
Brain	1

Once the exposure was completed, the tumour mass was dissected posteriorly from the psoas muscle, sympathetic nerves, vertebral bodies and aorta–IVC. In the course of this part of the operation lumbar arteries and veins were ligated and divided. The inferior mesenteric artery was ligated in nine patients. In five cases the tumour was encasing the renal vessels, necessitating unilateral nephrectomy; in one case the diaphragm was partially removed with the tumour (and repaired by primary closure); and in three cases the psoas was partially removed with the primary tumour. In one case the fourth part of the duodenum was resected and reanastomosed. The patient with an aortic graft *in situ* underwent careful dissection of residual tumour from around the graft without the need for graft replacement.

Metastatic disease that was apparent at the time of surgery was removed. Superficial liver metastases were removed by wedge resection. Retrocrural lymph nodes were removed through the chest. Lung metastases were resected using the TA 30 V3 (AutoSuture, Ascot, UK) stapling device.

At the end of the procedure two retroperitoneal suction drains, a chest drain, and an intrapleural cannula, for administration of local anaesthetic, were inserted. The wound was closed in layers with absorbable sutures.

Results

Complete macroscopic tumour clearance was achieved in all patients without perioperative complications, apart from haemorrhage requiring blood transfusion in all cases. Median blood loss was 2·5 (range 1·5–5) litres. There was no operative mortality. One patient who was ventilated over the first postoperative night developed a chest infection, which responded well to physiotherapy and antibiotics. The histology of the resected retroperitoneal tumours and metastases is shown in *Table 2*. In all cases in which malignant tissue was present it was confined to internal parts of the mass and was surrounded by necrosis and fibrosis following chemotherapy. Hence the surgical margins were clear in all cases.

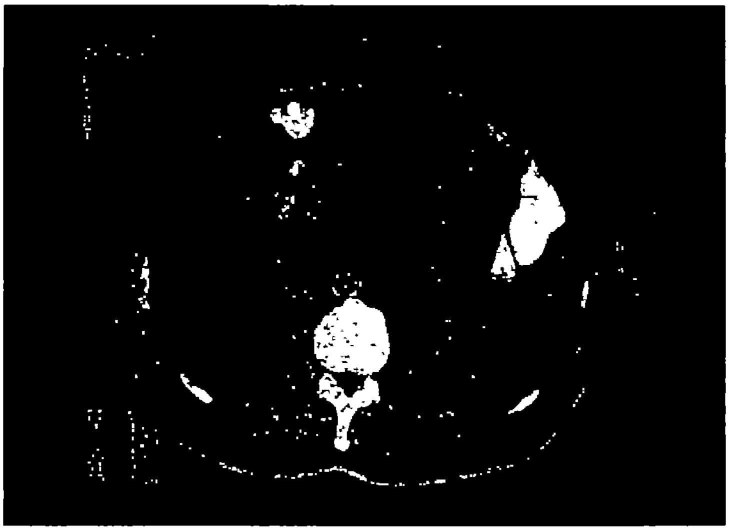

Fig. 1 Computed tomogram of a primary retroperitoneal germ cell tumour after chemotherapy and before complete surgical excision

Table 2 Histology of retroperitoneal tumour after chemotherapy

Histology of tumour	*n*	NED
Teratoma differentiated	5	2
Teratoma differentiated with yolk sac tumour	1	1
MTU	3	3
MTU and neuroectodermal tumour	1	1
MTU with liposarcoma	1	1
Necrotic tumour	3	3

NED, no evidence of recurrent disease on follow-up; MTU, malignant teratoma undifferentiated

In the early postoperative period the concentration of tumour markers remained within the normal range. None of the patients developed paralytic ileus. Median inpatient stay was 7 (range 6–10) days.

The median follow-up period was 15 (range 3–36) months. One patient who died 16 months after surgery, having developed a brain metastasis with positive tumour markers at 14 months, was treated with two courses of chemotherapy and then a craniotomy and tumour removal. Although the tumour markers returned to a normal level after neurosurgery, he died from multiple cerebral infarcts presumed to be secondary to bacterial encephalitis. One patient developed a liver metastasis at 10 months, which was treated by segmental resection. Tumour marker levels gradually increased 6 months after operation in one patient, who was treated with further chemotherapy and autologous bone marrow transplantation. The other 11 patients are under close surveillance; they have normal tumour markers and no evidence of recurrent disease. Hence, the current survival rate in this series was 13 of 14 and the postoperative disease-free survival was 11 of 14.

Late complications included loss of ejaculation in three patients, all of whom had had extensive dissection anterior to the bifurcation of the aorta. The patient who had lost ejaculation before operation noticed no change after surgery.

Discussion

The dramatic improvement in survival in patients with malignant non-seminomatous germ cell tumours has stimulated detailed analysis of series to identify subgroups with a poor prognosis. A number of staging and prognostic classifications have been proposed and the authors analysed their earlier series in detail using seven different prognostic systems[5]. In this series of 206 consecutive male patients, the initial serum concentrations of hCG and AFP appeared to provide as good a prediction of survival outcome as more complex systems. The Medical Research Council (MRC) Testicular Tumour Group has performed two detailed analyses of multicentre results from the UK[8,9]. The more detailed second MRC analysis of 795 patients treated between 1982 and 1986 identified six independent adverse features: (1) the presence of liver, bone or brain metastases; (2) AFP level greater than 1000 kU/l or hCG concentration above 10 000 IU/l; (3) mediastinal mass greater than 5 cm; (4) presence of 20 or more lung metastases; (5) increasing age; and (6) absence of undifferentiated teratoma (embryonal carcinoma or fibrous tissue in the primary tumour). The first four variables were recommended as useful for defining poor-risk prognostic groups, and the survival rate in groups who had none of the first four features was 92 per cent at 5 years. Where one of the features was present, the 5-year survival rate was 71 per cent; where two features were present, the rate was 48 per cent; and where three were present, it fell to 26 per cent. In this earlier series patients with a retroperitoneal EGCT had a poor prognosis, with survival in 12 of 33.

Primary retroperitoneal EGCT often presents late because the location allows the lesion to reach a large size before the onset of symptoms. Some of these tumours, particularly those with sarcomatous changes, fare badly with operation alone, especially if resection is incomplete[10]. Retroperitoneal EGCTs are eminently treatable and optimal results, as reported here and elsewhere[11], can be achieved by surgical resection of residual masses after chemotherapy. It is crucial to consider the diagnosis at an early stage to avoid premature unnecessary surgery and to commence chemotherapy promptly.

Tumour marker levels were raised in most cases and these should be measured in all men presenting with a retroperitoneal mass, regardless of age or the presence of normal testes on palpation and ultrasonography. Increased levels of tumour markers should prompt biopsy of the mass under CT or ultrasonographic guidance. Histological examination of such biopsies may be difficult to interpret. However, it has been suggested that all such cases should be treated as for retroperitoneal EGCT, especially if tumour marker concentrations are raised[4].

The success of the present series appears to relate to a combination of intensive alternating chemotherapy regimens[7,11] and subsequent surgical technique for removal of residual masses. Tumour markers are useful in monitoring the response to chemotherapy. However, when levels of tumour markers return to the normal range after chemotherapy and residual masses remain, it is still advisable to perform surgical excision because differentiated teratoma or malignant tumours such as sarcomas, which do not secrete markers, may be present.

In previous reports EGCTs have been removed through midline, transverse or oblique transperitoneal approaches[4,12–15]. There are advantages to the thoraco-abdominal extraperitoneal approach compared with transperitoneal operations. First, this approach allows removal of the primary tumour more readily, especially from behind the aorta–IVC and superior to the renal vessels. Second, intrathoracic extension as direct invasion through the diaphragm or lymph node and pulmonary metastases can be removed without the need for subsequent thoracotomy. Third, the extraperitoneal approach avoids the paralytic ileus that may prolong recovery and inpatient care after transperitoneal operations[6].

Ejaculatory dysfunction is likely to occur after excision of large tumour masses from around the bifurcation of the aorta and after division of sympathetic nerves on both sides of the aorta–IVC[16]. This occurred in four patients in this series, although one had lost ejaculation before operation, and hence loss of ejaculation attributable to surgery occurred in three of 13 patients. Bearing in mind the large dimensions of the tumour masses, this is a remarkably low incidence of postsurgical ejaculatory dysfunction. The authors believe that the thoraco-abdominal technique, by virtue of its lateral approach to the aorta–IVC, is less likely to cause ejaculatory dysfunction due to bilateral sympathetic nerve damage than anterior approaches.

The optimal treatment for retroperitoneal EGCT is intensive chemotherapy followed by surgical resection of the residual mass. The thoracoabdominal extraperitoneal approach has distinct advantages over anterior transperitoneal approaches for the removal of these tumours and their metastases.

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British Journal of Surgery 1997, 84, 1026–1034

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Retroperitoneal endoscopic neurectomy for nerve entrapment after hernia repair

Letter 1

Sir

I read with interest the recent paper by Dr Krahenbuhl *et al.* (*Br J Surg* 1997; 84: 216–19). This article attempts to give information about a solution for a special problem and highlights the condition of entrapment neuralgia after endoscopic hernia repair.

I have two objections to the reported conclusion and discussion. It does not make clear that injuries to the lateral femoral cutaneous nerve or the femoral nerve, recently occurring after laparoscopic hernia repair, are avoidable through open or conventional surgery.

Overall outcome for different important endpoints seem to be comparable with open (tension-free) hernia repair, but laparoscopic hernia repair can be associated with new and rare, but disastrous, entrapment syndromes.

For ethical reasons I am convinced that a surgeon should avoid any procedure with rare but disastrous events and choose an alternative approach with a comparable outcome. For hernia repair it is perfectly clear that there are some.

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Letter 2

Sir

We read with interest the article from Dr Krähenbuhl *et al.* (*Br J Surg* 1997; 84: 216–19) and congratulate the authors on their innovative idea of using the retroperitoneal laparoscopic approach for nerve entrapment. We advocate, however, a more limited indication for retroperitoneal endoscopic intervention.

The authors report three patients with successful results from retroperitoneal endoscopic neurectomy, without previous attempts at open nerve repair They suggest that if the genitofemoral nerve is damaged after open hernia repair, the first attempt at treatment should be lumbar neurectomy and that if an entrapment phenomenon does not diminish within 4–8 weeks of laparoscopic hernia repair, laparoscopic re-exploration with removal of the staples can be helpful. If pain persists for over 3 to 4 months, neurectomy is recommended. We believe the initial surgical management of entrapment neuralgia, regardless of whether the hernia repair is performed in an open or laparoscopic fashion, should be open revision to attempt nerve reconstruction Depending on the condition of the nerve and its surrounding wound bed, neurolysis, neuroma resection, nerve grafting or microsurgical-nerve coaptation should be performed before the last option of neurectomy. Nerve resection can lead to repeat neuroma formation resulting in chronic pain. Numbness, which the authors describe as 'insignificant morbidity', can be very debilitating and should not be overlooked. Identifying the affected nerve endoscopically can be difficult due to scarring from previous operations, anatomical variations and limited operative view

We suggest trying all conventional open methods for peripheral nerve treatment, with retroperitoneal endoscopic nerve entrapment as a last option.

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Authors' reply

Sir

We thank Professor Troidl and Dr Schoeller and colleagues for their interest in our paper and for raising some important points that we agree need further discussion.

The two objections raised by Professor Troidl are that injury to the lateral femoral cutaneous nerve and the femoral nerve reported after laparoscopic hernia repair can be avoided using conventional hernia repair, and that due to different 'endpoints' (entrapment and increased costs for laparoscopic hernia repair) open hernia surgery (i.e. tension-free) should be preferred. As mentioned in our article, entrapment neuralgia after open and laparoscopic hernia surgery may occur in about 1 to 2 per cent. Following open surgery (Bassini, Shouldice or tension-free), entrapment symptoms from the genital branch of the genitofemoral nerve and the ilioinguinal nerve are reported, whereas after laparoscopic surgery damage to the femoral branch of the genitofemoral nerve occurs more frequently. Entrapment of the lateral femoral nerve and even of the femoral nerve is rare In a recent multicentre study by Felix *et al.*[1] only 15 (0·2 per cent) nerve entrapments among 8230 laparoscopic hernia repairs were reported. The aim of our report was to outline that entrapment symptoms with significant morbidity occur after open and laparoscopic hernia repair, and to describe a new surgical treatment (endoscopic retroperitoneal approach) to the most frequently damaged genitofemoral nerve (genital and femoral branch) following conventional or laparoscopic hernia repair. Using this approach in selected cases (twice after laparoscopic, once after open hernia repair) complete pain relief has been achieved. The point raised by Professor Troidl that for ethical reasons tension-free repair is the procedure of choice for groin hernia surgery is a misunderstanding: to answer the question of which procedure is best for treating inguinal hernia was not the aim of the article. However, we do not support his opinion that the tension-free repair is the procedure of choice for treating all types of inguinal hernia.

Dr Schoeller and colleagues are quite right that after open hernia repair and nerve damage open revision and an attempt at nerve reconstruction should be attempted first, but only in the case of ilioinguinal nerve entrapment[2]. In most cases of genitofemoral nerve damage, open *retroperitoneal* neurectomy was needed at the second attempt to achieve complete pain relief. Severe pain after herniorrhaphy can lead to debilitation and occupational incapacitation. Therefore, pain relief should be the ultimate goal for treating patients with entrapment neuralgia.

In the case of genitofemoral entrapment the question for debate is why a local neurolysis, neuroma resection or nerve grafting with overall unsatisfactory results (persistent dysthesia) should be performed when, by using the described (endoscopic) lumbar neurectomy with its associated insignificant morbidity, complete pain relief in more than 90 per cent of cases can be achieved[2]. Little has been written about the surgical treatment of entrapment neuralgia following laparoscopic hernia repair. By using a preperitoneal mesh, local neurolysis or nerve reconstruction as well as laparoscopic removal of the staples is rendered impossible due to the fibrous tissue reaction after 2 to 3 weeks after surgery, and local neurolysis or nerve reconstruction does not solve the problem because of the initial retroperitoneal approach. Therefore, in selected cases (confirmed diagnosis as described in the article) the new endoscopic retroperitoneal approach which is easy to perform (no scarring from previous surgery) might offer a better therapeutic option for complete pain relief.

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Prospective randomized trial of clips *versus* subcuticular polydioxanone for neck wound closure

Sir

While we would not dispute the conclusion that subcuticular polydioxanone achieves a cosmetically acceptable result comparable to that of skin clips we were interested to note that the only significant difference between the two groups in this randomized study (*Br J Surg* 1997; **84**: 118) was the length of stay (5·9 days for clips *versus* 4·2 days for polydioxanone). The practice of keeping patients in hospital until skin clips are removed on the fourth day is obsolete and we have described on a number of occasions the policy of routine removal of skin clips (or staples) and discharge from hospital on the first postoperative day. This has been the practice in Aberdeen for more than 20 years. There may be reasons for some patients to remain in hospital for more than 1 day such as advanced disease, calcium homeostasis or social reasons.

The data audited prospectively on 441 consecutive patients undergoing thyroid surgery in our unit between January 1991 and December 1996 is shown below·

Postoperative day of discharge	Number	Per cent
First	282	64·0
Second	96	21·8
Third	26	5·9
Fourth	14	3·2
Fifth or greater	23	5·2

The mean length of stay for these patients was 2·9 days, with a mean stay after operation of 1·8 days. We would commend this practice to surgeons with an interest in thyroid surgery and disagree that the use of a subcuticular suture contributes to more efficient management.

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Author's reply

Sir

We thank Messrs Krukowski and Matheson for their interest in our paper and agree that the Aberdeen data are impressive.

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Genetic testing is important in families with a history suggestive of hereditary non-polyposis colorectal cancer even if the Amsterdam criteria are not fulfilled

Sir

I read with interest the article by Mr Beck *et al.* (*Br J Surg* 1997; **84**: 233–7). I agree with the authors that genetic testing in hereditary non-polyposis colorectal cancer (HNPCC) should not be limited only to families fulfilling Amsterdam criteria[1]. As pointed out by the authors the criteria help identify high-risk families for analyses which subsequently identify the DNA mismatch repair gene mutations in HNPCC. Clinicians must be aware, however, that mutations occur in families not meeting these criteria.

The authors state that identification of a germline mutation in an individual gives the prospect of prophylactic surgical intervention that could be curative. This is not accurate. The penetrance in HNPCC is not 100 per cent and not every individual carrying a germline mutation will develop colorectal cancer. A prophylactic procedure decreases the risk of cancer in the target organ, but does not eliminate it. In HNPCC and other inherited disorders such as breast and ovarian cancer, prophylactic surgery may not be curative. Cancers may develop after prophylactic mastectomy and oophorectomy[2,3]. After surgery for familial adenomatous polyposis cancer has developed at the ileoanal anastomosis and in the ileoanal pouch after restorative proctocolectomy[4,5].

Because of the increased incidence of synchronous and metachronous lesions, the treatment of choice for an individual with HNPCC and colon cancer is a colectomy with ileorectal anastomosis[6]. Prophylactic colectomy in HNPCC has been advocated as a potential option in gene carriers with a completely normal colon[7] as well as an alternative to endoscopic polypectomy in mutation carriers[8]. An abdominal colectomy leaves rectal mucosa at risk. The risk of rectal cancer in HNPCC 12 years after an abdominal colectomy is 12 per cent[9]. A prophylactic abdominal colectomy may not be curative. Even if a restorative proctocolectomy is performed, it is not curative in HNPCC because, as stated by Beck *et al.*, extracolonic malignancies occur in these patients

The questions remain: prophylaxis of what? And what are we curing?

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Author's reply

Sir

Dr Rodriguez-Bigas highlights what will be an increasingly difficult dilemma as more germline defects are identified which predispose to cancer formation. In the case of HNPCC, identification of a germline mutation in an individual does give the prospect of prophylactic surgical intervention that could be curative. It is true that cure will not be possible in all patients and we did not claim otherwise. There are, of course, examples of cancers developing following prophylactic surgery in other conditions, but these are the exception rather than the rule. It is also true that, in a proportion of patients, prophylactic surgical intervention may be unnecessary, as the penetrance of HNPCC is not 100 per cent. The decision to offer a colectomy to an individual who has a germline mutation in one of the mismatch repair genes is not an easy one. However, as the understanding of genotype–phenotype correlations in HNPCC increases, so more informed choices will be able to be made. The objective of prophylactic surgery should be clear to both the surgeon and to the patient. A prophylactic colectomy aims to eliminate the risk of colon cancer and nothing more. None the less, such surgery could be curative.

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Extending the role of breast-conserving surgery by immediate volume replacement

Letter 1

Sir

I read with interest the recent publication by Dr Raja and colleagues (*Br J Surg* 1997; 84: 101–5). The goals of breast-conserving treatment (BCT) are to achieve local tumour control and survival rates equivalent to those of mastectomy while preserving an acceptable breast appearance. Although the technique of wide excision followed by breast irradiation provides adequate local control, it often yields poor cosmetic results, especially in patients with small breasts. To improve the cosmetic aspect after wide excision we proposed the immediate transposition of a latissimus dorsi muscle (LDM) flap in BCT[1,2]. Raja *et al.* report a modified technique that avoids a frontal scar and allows a wide retromammary excision via a lateral approach. The latissimus dorsi miniflap (LDMF) can be displaced anteriorly to lie in the breast resection defect, as reported previously[1,2] The results suggest that immediate volume replacement with LDMF reconstruction may avoid many of the cosmetic penalties associated with extensive local resection. These workers also reported that postoperative flap atrophy has been of theoretical concern, but adequate volumes of innervated muscle have been maintained for up to 4 years. I agree that routine excision of overlying skin is unnecessary except for superficial lesions and a frontal scar can be avoided using their technique. One problem, however, involves atrophy of the transposed LDMF[3] and a sufficient volume of adipose tissue must be transposed in addition to the LDMF[4,5]. The cosmetic result has been much improved by transposition of increased amounts of adipose tissue[5]. The group have recently been using an endoscope to increase the amount of tissue mobilized (personal communication, R. M. Rainsbury). In the present study by Raja *et al.* as well as a previous report[4], a substantial reduction in margin positivity was observed, reflecting the wider resection that can be achieved with immediate volume replacement. With these improved surgical techniques, it is hoped that BCT will become a more acceptable treatment option for the majority of patients with operable breast cancer.

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Letter 2

Sir
We read with interest the article by Mr Raja *et al.* (*Br J Surg* 1997; **84**: 101–5) which addressed the important subject of primary partial breast reconstruction after wide excision of breast malignancy. We applaud the desire to improve the cosmetic outcome of such procedures but a number of important points require comment.

The first relates to true cosmesis which must be considered to be more than just a mathematical, visual attribute (which is what was measured). The suppleness of the reconstructed breast is as important as appearance when undertaking reconstruction[1]. Measurements of the retraction of the nipple were assessed with the patient immobile. As the muscle flap was left innervated, nipple retraction should perhaps have been assessed following contraction of the pectoral girdle as nipple retraction or deformity during use of the arm might distress some patients.

The recognized complication of brachial plexopathy or Parsonage–Turner syndrome may comprise pain and burning in the shoulder and neck area to weakness of the serratus anterior[2]. Although this occurred in only one patient in this series (5 per cent) it is rather disabling.

It is unfortunate that the discussion did not address the alternative procedure of the use of gel filled implants to replace volume loss in the breast.

A major criticism, however, relates to the failure to comment on the patients' satisfaction with the procedures which could have used the same degree of rigour to achieve a true and comprehensive assessment.

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Author's reply

Sir
We thank Mr Khan and colleagues for highlighting some of the important issues raised by immediate volume replacement after partial mastectomy. First, although the suppleness of the reconstructed breast is all important, a reproducible technique for the measurement of breast consistency after partial reconstruction has yet to be developed. Unlike reconstruction using synthetic prostheses, autogenous tissue replacement is free from the problems associated with implants, such as silicone bleed and capsule formation. These can lead to progressive local distortion and disfigurement, impeding the detection of local recurrence and the mammographic visualization of the surrounding breast tissue[1]. Autogenous volume replacement circumvents these problems by providing a 'life-like' tissue substitute. This facilitates postoperative mammographic surveillance by reducing the formation of stellate-shaped radiodense scars which may lead to confusion, misinterpretation and unnecessary intervention following conventional breast conserving surgery[2].

Second, flap contraction within the breast is a feature common to all types of reconstruction using innervated muscle, including subpectoral and partial or complete latissimus dorsi reconstruction. This can be avoided by routine transection of the thoracodorsal nerve at the time of reconstruction, or at a later date, although this is rarely requested.

Third, it is vital to prevent overabduction of the arm in order to avoid brachial plexopathy by securing it to a fixed point such as a Lloyd-Davies stirrup. We have now performed more than 60 procedures without a further case of brachial injury using this technique.

Finally, the purpose of the study was to evaluate the surgical, oncological and cosmetic outcome of a technique which may extend the indications for breast conservation. A separate investigation of patient satisfaction is underway, in which a number of other aspects of this approach will be investigated, including the value attached to a procedure which may avoid mastectomy.

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Osmotic therapy for acute irreducible stoma prolapse

Sir
I read with interest the paper by Mr Fligelstone *et al* (*Br J Surg* 1997; 84: 390). They have highlighted an ingenious, yet simple and cheap method for the treatment of acute irreducible stoma prolapse. This is, however, an established technique.

Granulated sugar has been used for many years by veterinary surgeons in the treatment of various types of prolapse in animals including cow, horse, dog and cat[1,2]. More recently Myers and Rothenberger reported this osmotic technique in treating patients with rectal prolapse and incarcerated prolapsed colostomies and ileostomies[2].

The desiccating effects of table sugar, which are well illustrated in the recent paper should be borne in mind when confronted with incarcerated, prolapsed viable bowel presenting rectally or through a stoma.

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High prevalence of *Helicobacter pylori* infection in duodenal ulcer perforations not caused by non-steroidal anti-inflammatory drugs

Sir
We read with interest the article by Dr Ng *et al* (*Br J Surg* 1996; 83: 1779–81) The authors recommend antimicrobial therapy to eradicate *Helicobacter pylori* infection in patients with perforated peptic ulcer not caused by non-steroidal anti-inflammatory drug usage and state that 'patients maintained on continuous acid suppressing agents may still develop recurrent ulcer sometimes

even with complications and the cost of prolonged maintenance treatment is considerable'. They doubt the value of maintenance treatment with acid suppressing agents.

We would like to point out that an anti-acid secretory agent should be used with antimicrobial agents as it acts synergistically to give eradication of the organism[1,2].

For eradication of *H. pylori* infection, different combinations of antimicrobial agents have been suggested (triple therapy with bismuth, metronidazole and amoxycillin or tetracycline) with varying success rates[3]. Bismuth, although an effective bactericidal agent, induces side-effects such as constipation and darkening of faeces. More serious adverse effects, such as encephalopathy and neurotoxicity may pose problems in patients with renal failure. The drug is not licensed for treating *H. pylori* infection[1].

Recent studies have indicated that effective total eradication of *H. pylori* can be achieved by using an antisecretory drug such as omeprazole or lansoprazole with antimicrobials like clarithromycin and metronidazole for one week[1,4].

Maintenance treatment should be considered when there is a history of life-threatening complications such as repeated bleeding or perforation and that the long-term maintenance treatment with H_2-receptor antagonist is safe[5]. A significant reduction in the ulcer relapse rate using H_2-receptor antagonists has been reported[6].

Continuous maintenance treatment with cimetidine for 6 years reduced the incidence of symptomatic peptic ulcer and its complications (stenosis, haemorrhage and perforation)[7]. Another H_2-receptor antagonist, famotidine, at low dose (20 mg at night) significantly decreased the incidence of duodenal ulcer relapse at 12 months while higher doses gave no advantage. The potency, lack of toxic effects such as acute overdosage or potentially life-threatening or irreversible adverse effects and uniformity of uptake, bioavailability and elimination make famotidine a potential H_2-receptor antagonist[8,9].

Famotidine is now affordable by many patients and makes the therapy cost-effective, especially in India. We suggest that the newer antisecretory agent lansoprazole be used with antimicrobial agents for eradication of *H pylori* in this situation and famotidine be used for long-term maintenance therapy.

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Authors' reply

Sir
We thank Drs Thulasimani and Ramaswamy for their comments. That long-term acid suppression is not required for uncomplicated ulcers after successful eradication of *H. pylori* is undisputed For patients with life-threatening complications such as bleeding, some authorities have recommended maintenance acid suppression in addition to eradication therapy[1]. Such recommendation is, however, not based on scientific evidence[2]. On the other hand, several studies, including two controlled randomized trials, indicated that recurrent bleeding does not occur if bacteria are eradicated[3–6]. There is less information on perforated ulcers. Our study provided circumstantial evidence that *H pylori* infection and NSAID usage may be two independent causes of perforated ulcers, and supports the premise of using antimicrobial therapy in those who are *H pylori*-positive. Whether such a policy reduces recurrent ulcers and prevents future complications awaits confirmation by controlled randomized trials. One such study is in progress in our Institute.

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Reduced collagen accumulation after major surgery

Sir
We read the paper by Dr Jorgensen *et al.* (*Br J Surg* 1996; 83: 1591–4) on the effects of major surgery on wound healing with interest.

In the trial the number of patients was insufficient to evaluate the effects of variables without adequate stratification of patients according to diagnosis, severity of disease, duration of surgery and malignancy. These factors may be significant in wound healing and influence the results of this study. A multivariate analysis could have been performed if a sufficient number of patients had been acquired. A recommendation of statisticians is to include ten times as many subjects as there are independent variables[1].

It is also important to take into account arterial blood gases and pulmonary function tests as predictors of tissue hypoxia which may also affect wound healing[2–4].

Infection or sepsis reduces local wound healing[5] and alteration in hydroxyproline levels in the study might be due to this effect[6] rather than the surgery itself. The analysis should have been performed after excluding patients with infective complications.

General anaesthesia has detrimental effects on the immune system[7] but the effect on wound healing is not known. In this 'before and after' trial, general anaesthesia may also have had an effect on wound healing and result in reduced collagen accumulation after major surgery. The type of anaesthesia used was not standard for the insertion of e-polytetrafluoroethylene tubes in the 'before and after' arms. For standardization it would be more appropriate to use local anaesthetic for inserting the tubes in the 'after' arm of the study. An animal experimental model might have allowed more standardized conditions such as type and duration of surgery and effect of general anaesthesia.

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Authors' reply

Sir

We thank Dr Agalar and colleagues for their interest in our article. The aim of the paper was to evaluate the wound healing response in patients undergoing major surgery which is not infrequently complicated by impaired wound healing. The study was descriptive and studied patients undergoing various procedures with standard perioperative care. We were not studying patients without complications. The number of patients was not suitable for multifactorial analysis or stratification into risk factor groups and this was specified in the paper. The patients acted as their own controls (paired observations) and, despite the limited number of patients included in the study, the postoperative decline of the amount of collagen deposited in the expanded polytetrafluoroethylene test wound was statistically significant.

We have clearly stated that we consider tissue hypoxia to be one of the key factors explaining the postoperative decline of the subcutaneous collagen accumulation. This has been intensively studied previously and measurement of tissue oxygen tension is preferred over arterial gas analyses and pulmonary function tests especially as the latter are only little affected by hypoperfusion[1–4].

We agree that a potential impact on the wound healing response from the use of general anaesthesia cannot be excluded but this was discussed in the paper. In wound healing research, results from animal studies cannot always be extrapolated to clinical practice and we believe that a study in humans applying a minimally invasive surrogate wound model is preferred.

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Ambulatory manometric examination in patients with a colonic J pouch and in normal controls

Sir

We read the article by Mr Romanos *et al* (*Br J Surg* 1996; 83. 1744–6) with interest and feel it raises important issues for the interpretation of these physiological studies.

'A stapled pouch–anal anastomosis was performed at a median of 3 (range 2·0–4·5) cm from the anal verge'. If this is correct, the upper segment of the internal sphincter would have been removed in a proportion of patients. The allocation of the lower two microtransducers (placed 1 cm apart) to upper and lower anal canal respectively is therefore difficult to achieve in some patients.

One patient had a mean pouch–rectal pressure of 74 cmH$_2$O. Such a value suggests that the microtransducer concerned had either prolapsed into the upper anal canal thus measuring sphincter pressure, or had been recording wall pressure.

Four patients complained of minor incontinence and had a lower pressure gradient than patients with continent pouches (eight observations), 39 *versus* 63 cmH$_2$O, $P = 0{\cdot}03$. Such small numbers make a Type 1 error likely and a Student's t test difficult to interpret.

In *Fig. 1* we are asked to accept that the external anal sphincter contracts to preserve continence (right hand arrow). If the contraction described is the short duration, small amplitude pressure rise then why do we see contemporaneous and apparently equal pressure rises in the upper anal canal and the pouch. A more reasonable explanation is that this represents movement artefact.

Fig 3 illustrates the difficulty in interpreting physiological observations in dynamic situations (defaecation). The absence of all but one contraction (interestingly the lower pressure transducer) in the pouch during the first 10 min of defaecation suggests that the catheter has either fallen out or is not recording accurately. Could the anal canal microtransducers be recording atmospheric pressure at this point?

The clinical results in this series are encouraging to those considering this operative approach to low rectal cancer but care must be taken to avoid overinterpretation of results in ambulatory anorectal manometry studies.

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Authors' reply

Sir

We were interested to read the comments by Messrs Macdonald and Sunderland on our paper.

One woman in the series had a very low tumour with an anastomosis at around 2 cm from the anal verge. In some women the anal canal is very short, as in this case, and a small portion of internal anal sphincter might have been resected Probe placement was achieved live with real time read out of pressures on the display screen ensuring accurate positioning. Any periods of displacement were omitted from analysis.

The single patient with a pouch pressure of 74 cm had a pouch emptying problem. Patients were not prepared and if stool was still present in the pouch this would contribute to this unusually high pressure. We agree, therefore, that there may have been some error.

We accept the criticism of a possible Type 1 error but these are difficult studies in patients with a rare problem and we hope to verify these findings with a future larger study

The short duration pressure rise mentioned in *Fig. 1* is artefactual; it is present in all four traces and the figure is too small to see the subsequent pressure rise.

During defaecation the probe was usually expelled so the area described is, of course, due to expulsion and this was excluded from the analysis.

This is not an easy field of study but we accept the criticism and look forward to seeing the contributions from others in due course.

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Benefits of D_2 lymph node dissection for patients with gastric cancer and pN_0 and pN_1 lymph node metastases

Sir

I read with interest the recent article by Professor Siewert *et al.* (*Br J Surg* 1996; 83: 1144–7). In a previous retrospective study[1], they reported that patients with Union Internacional Contra la Cancrum (UICC) tumour stages II and IIIA benefit from radical (D_2) lymph node dissection. In the subgroup analyses, the survival advantage was most pronounced in patients with absent (pN_0) or early (pN_1) lymph node metastasis on routine histological examination. In the present study, they performed immunohistological analysis of 100 patients with $pT_{1-3}N_0$ and $pT_{1-3}N_1$ gastric adenocarcinoma who underwent radical (D_2) lymph node dissection and demonstrated a high frequency of microinvolvement. The presence of microinvolvement was identified as an independent prognostic factor in multivariate analysis. They suggested that this is one reason why patients benefit from radical lymph node dissection even if the removed lymph nodes are not involved by tumour (pN_0) on routine histological examination. I agree that the presence of microinvolvement in the lymph nodes is frequent and may be a prognostic factor. In their previous study[1], however, the removal of 26 or more nodes was defined as a radical lymph node dissection (D_2 resection), while extirpation of fewer than 26 nodes was considered standard lymph node dissection (D_1 resection). There was a mean of 15·4 removed lymph nodes in patients who underwent standard lymph node dissection, while the radical lymph node dissection resulted in removal of a mean of 45·4 nodes. It is known that extended lymph node dissection results in substantial stage migration[2] We found that the distribution of UICC tumour stages in their previous study differed significantly between patients who underwent standard and those who underwent radical lymph node dissection ($P < 0{\cdot}0001$)[1]. A standard lymph node dissection may not be enough to detect lymph node metastases, even though it removes 15 or more nodes It is possible that the observed differences in survival resulted from the understaging of the extent of disease in patients who underwent the standard lymph node dissection. Although many Japanese surgeons are hopeful that the extended lymph node dissection improves the survival of patients with gastric carcinoma, we await the final results of prospective randomized clinical trials involving a large number of patients[3].

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Author's reply

Sir

This is a very nice letter but it contains no new aspects. The topic of stage migration has been discussed frequently and we answered a similar letter to the editor regarding this topic[1]. I think it unecessary to give another answer to the same question.

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Surgical aspects of *Clostridium difficile* colitis

Sir

The Review by Messrs Bradbury and Barrett (*Br J Surg* 1997; 84: 150–9) clearly explains surgical aspects of *Clostridium difficile* colitis. It fails, however, to report two simple and well documented approaches to prevention of *C. difficile* infection, both of which we have implemented in Exeter, UK.

First, patients receiving antibiotics for more than 48 h and patients with diarrhoea awaiting results of a *C. difficile* toxin test, are commenced prophylactically on Phillip's Brewer's Yeast (two tablets, four times per day, Phillip's Yeast Products, London, UK). Brewer's Yeast contains the dead form of *Saccharomyces cereviseae* (synonymous with *Saccharomyces boulardii*) which probably acts by altering bowel flora, binding *C. difficile* toxin and increasing local immunoglobulin A production. Several publications recommend its use and the only reported side-effect in immunocompetent patients is that some find it unpalatable[1,2]. The cost of Brewer's Yeast is about three pence per patient per day

Second, live yoghurt, which contains Bifidobacteria, is now supplied by the hospital for all patients except those with neutropenia. *Bifidobacterium longum* is part of the normal human intestinal microflora and, when administered as biotherapy, it is thought to re-equilibrate intestinal flora[3,4].

These simple and inexpensive measures are safe and easy to implement. We believe that they may encourage the return of normal bowel flora in patients on surgical wards which should protect against overgrowth of gut pathogens such as *C. difficile*.

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Rectus sheath bupivacaine analgesia after aortic surgery

Sir

We read with interest the paper by Mr Curley and colleagues (*Br J Surg* 1996; 83: 1558) highlighting the value of intermittent bupivacaine analgesia after aortic surgery through a transverse incision. While there is no comment made regarding the efficacy in terms of pain relief, one assumes that this has been found to be satisfactory. The experience of one of us (R.J.C) using this technique for postoperative pain control following upper abdominal surgery has not been as rewarding Eighty patients undergoing cholecystectomy were allocated randomly to receive either bupivacaine 0·5 per cent or normal saline by infusion over a 60-h period. There was no significant difference in the severity of pain (linear analogue pain scores), arterial oxygen tension or peak expiratory flow rate during the first 4 days after operation[1]. By contrast, in a further randomized study of patients undergoing cholecystectomy the use of thoracic epidural analgesia with bupivacaine 0·5 per cent commenced intra-operatively and continued for 12 h after operation produced significantly better pain relief within the first 12 h when compared with patients receiving intermittent intramuscular opiates. This was associated with a significantly higher arterial oxygen tension and a significant reduction in the incidence of chest infection[2]

During the past 5 years at Doncaster Royal Infirmary we have used regional analgesia in 250 patients undergoing vascular reconstructions. The technique varies according to whether the procedure involves the aortoiliac segment or is limited to the subinguinal vasculature. In the former we use a combination of general anaesthesia and epidural anaesthesia, the epidural catheter being placed in the thoracic region at T9/10 level Initially 10 ml of bupivacaine 0·5 per cent and 100 μg of fentanyl are infused at the time of surgery reducing to bupivacaine 0·1 per cent with 10 μg per ml of fentanyl at the rate of up to 8 ml per hour using a syringe driver depending on the pain scores after surgery. Subinguinal surgery is performed entirely under regional analgesia using an epidural spinal technique, 2·5 ml of bupivacaine 0·5 per cent being given intrathecally and a further 7 ml of bupivacaine 0·5 per cent plus 100 μg of fentanyl infused through an epidural catheter. More recently we have continued the epidural infusion in these patients for 24 h after surgery in the light of recent evidence that epidural anaesthesia and analgesia is associated with a reduction in vaso-occlusive events.

Both these techniques are effective for pain control but they have not been evaluated for graft occlusion rates because of an absence of controls. All patients are nursed on the high dependency unit and a strict protocol is followed. We have not encountered any major complications

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Author's reply

Sir

We thank Mr Cuschieri and Dr Raithatha for their comments They eloquently state the argument that we espouse, that critical comparison between an established and a new analgesic regimen must be made. Our article recommends comparison between epidural analgesia and the rectus sheath technique. It is important to point out that the technique described differs in three ways from that used by Gibbs *et al.*[1] and Cuschieri *et al.*[2]. (1) The technique is used after a transverse incision, which has been shown to be less painful than midline or paramedian incisions. (2) Catheters are placed bilaterally ensuring all involved peripheral nerves are exposed to bupivacaine. (3) The use of a Redivac (Biomet, Bridgend, UK) tube with side holes allows bupivacaine to perfuse over a larger area than when delivered via an epidural catheter. Despite these comments Cuschieri and colleagues have scientifically assessed the technique they have described and found it wanting when compared with epidural analgesia. They are to be congratulated on the achievement which is one we hope to emulate.

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Endorectal repair of rectocoele revisited

Sir

With reference to the recent publication by Dr Khubchandani *et al.* (*Br J Surg* 1997; 84: 89–91), we believe that rectocoele is one manifestation of a poorly understood complex disorder of pelvic floor failure.

(1) While obstructed defaecation is a prominent associated symptom, many patients present with a lump in the vagina without any anorectal symptoms. Forty-three of 75 (57·3 per cent) patients that we have studied had a vaginal repair performed by gynaecological colleagues Only 28 per cent of this group had obstructed defaecation while the remaining 72 per cent presented with a 'lump in the vagina'. Fifty-eight per cent reported improvement in symptoms of obstructed defaecation while 86 per cent reported a cosmetic improvement. These results suggest that vaginal repair should be restricted to rectocoeles without obstructed defaecation.

(2) Unlike the authors, we plicate the rectocoele endoanally with a running suture of 2/0 polydioxanone. Twenty-eight per cent of the cohort gorup had this performed with 85 per cent 'cosmetic' improvement and 76 per cent relief of obstructed defaecation. Over a mean period of 16 (range 14–18) months we have not observed any rectovaginal fistulas. Simple plication may be preferable to the flap procedure being effective, less traumatic and repeatable.

(3) In the presence of a bad obstetric history (such as forceps delivery and baby weight of more than 4 kg), rectocoele is often associated with sphincter failure. This group underwent a transperineal approach, separating the entire rectocoele from the posterior vaginal wall (with sagittal splitting of the vaginal wall if necessary to access the supralevator plane). After plication of the rectocoele, a levatoplasty was performed with repair of the sphincters. Fifty-eight per cent of patients in this group had relief of obstructed defaecation.

The management of rectocoeles should be dictated by previous obstetric history, findings on the defaecating proctogram, colonic transit study and endoanal ultrasonography scan. A comprehensive prospective study based on these parameters is necessary before advocating a treatment plan for what may be a heterogeneous group of pelvic floor disorders.

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Book reviews

Churchill's Mastery of Medicine. Surgery I

M. Lavelle-Jones (ed.). 296 × 209 mm. Pp. 207. Illustrated. 1996. Edinburgh: Churchill Livingstone. £15.

This slim volume covers 11 subjects in surgery and is aimed primarily at the final year student who is preparing for examinations. The book is concisely and very clearly written, and the most pleasing aspect is a strong emphasis on examination technique. At the end of every chapter there are excellent self-assessment questions in the form of multiple choice questions (MCQs), case histories, short notes and figures. All questions are well constructed and of the standard encountered in finals, although I do think that the MCQs in transplantation and cardiac surgery are quite testing. Of the various topics covered, all are written to a high standard and clarity is the keynote. The chapter on cardiac surgery is detailed and interesting, and covers 26 pages. Neurosurgery is also of a high standard and covers 13 pages. However, only one-quarter of a page is devoted to wound infection and general principles, and only two pages are devoted to trauma. Perhaps being slightly picky, I was disappointed not to find any mention of the assessment of the severity of acute pancreatitis. The role of elective surgery for peptic ulcer disease seemed rather out of date and I was disappointed not to find testicular tumours as a cause of gynaecomastia. However, these are very minor points. I believe that this book fills a niche market, supplying a detailed revision programme for the student who is about to revise for his or her surgical final. The final year students who are attached to our unit all gave the book a high rating.

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Surgery – A Clinical Approach

F. S. Bongard, M. J. Stamos and E. Passaro Jr (eds). 278 × 215 mm. Pp. 631. Illustrated. 1997. New York: Churchill Livingstone. £35.

With expanding surgical knowledge and a streamlined medical student curriculum the demand for a 'concise but complete' introductory textbook of general surgery has never been greater. This book from the UCLA School of Medicine is the latest attempt to fill this gap in the market, covering not only general surgery but also the main surgical subspecialties. In a drive to remain concise, the authors set out to stress principles and concepts rather than the acquisition of data. The strength of the book follows on from this, with a text that is succinct and easy to read, including useful case studies and key point summaries that nicely emphasize the take-home messages. The line drawings are generally clear although sparse in number. It is easy, therefore, to scan fairly rapidly at a superficial level across the spectrum of surgery and its specialties, taking in principles and key points. The chapters on care of the surgical patient, including critical care, oncology and surgery in patients with AIDS, are particularly strong. Inevitably, in-depth factual knowledge is missing, and unfortunately the book is weak on clinical symptoms and signs that are so fundamental to medical student training. To remedy the lack of factual data a CD-Rom is provided with the volume, containing the text and access to Medline North American surgical abstracts; but I doubt if many medical student readers would find this a very user-friendly medium for obtaining more detailed information. Medical student surgical texts increase in number every day and the choice is now wide. This book's niche is very much at the introductory end of the scale where it performs well, but a supplementary text on clinical symptoms and signs is also required.

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Laparo-Endoscopic Surgery. 2nd ed.

I. B. Brune (ed.). 279 × 215 mm. Pp. 402. Illustrated. 1996. Oxford: Blackwell Science. £79.50.

This book has the ambition to describe all laparoscopic and endoscopic thoracic and abdominal surgical procedures. It also provides sections on history, development of instruments, and errors and risks with pneumoperitoneum. The different procedures are grouped according to area: biliary tract surgery, oesophageal and gastric surgery, colonic and rectal surgery, paediatric surgery etc. The text describing the different procedures is most often, but not always, supported by good illustrations and photographs. There is generally no evaluation of the procedures by the authors, merely a description of what is possible. Data, such as indications for surgery, number of patients who have undergone surgery, short- and long-term outcome, and comparisons with other treatment technologies, are most often not provided. As is often the case in multiauthor books, there are significant differences between chapters in exposition as well as in the quality of the description and illustration of the procedures. Each group of procedures is briefly commented on by a distinguished surgeon not personally involved in developing laparoendoscopic surgical procedures. Such evaluation is more the personal opinion of the commenting surgeon than an evaluation based on established data. This book might serve as a catalogue of surgical laparoendoscopic procedures, but this area is developing rapidly and its value is likely to be fairly short-lived. The lack of serious evaluation makes this volume less useful for the inexperienced surgeon.

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Maingot's Abdominal Operations. 10th ed.

M. J. Zinner, S. I. Schwartz and H. Ellis (eds) Both volumes: 285 × 215 mm. Pp. 2200. Illustrated. 1997. Connecticut: Appleton and Lange. £195.

This is the latest edition of a surgical text that has become well known to virtually all practising surgeons. In an era of increasing specialization in surgery and a plethora of specialist surgical texts, the role of a book such as this, which covers a wide spectrum of pathologies and specialties, might be questioned. However, this volume is of a very high standard. In fact, some topics are covered in more appropriate and precise detail here than they are in some specialist surgical texts. The book has been very carefully edited to reflect changes in investigation and management of abdominal pathology, particularly the developments in diagnostic and minimally invasive procedures, including endoscopy and laparoscopy Each topic is covered by authors who are internationally recognized, giving an up-to-date representation of appropriate investigation and management techniques. The authors have succeeded admirably in providing an excellent general abdominal surgical textbook which is extremely appropriate and useful, not only for surgical residents or trainees but also for all practising general surgeons.

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Cardiovascular and Vascular Disease of the Aorta

L. G. Svensson and E. S. Crawford. 285 × 215 mm. Pp. 472. Illustrated. 1997. Philadelphia, Pennsylvania: W. B. Saunders. £107.

Dr E. Stanley Crawford's experience with complex aortic diseases is a whole order of magnitude greater than that of any other vascular surgeon, past or present. Who else could have reported a series of 1509 consecutive thoracoabdominal aneurysm repairs spanning a period of 31 years and achieved an overall 30-day survival of 92 per cent? That enormous experience has now been distilled into a single volume. The strength of the book is probably best summarized by Dr Crawford's co-author and colleague, Dr Svensson, when he says in the preface 'while many experts could have written in great depth the individual chapters for this book, we believe that there is virtue in describing a unified approach to the management of aortic disease based on our experience'. The book is comprehensive, well written and beautifully illustrated throughout with angiograms, scans of various sorts, and high-quality line drawings illustrating the authors' techniques and innovations I am sure this book will be widely recognized as one of the greatest literary contributions to vascular surgery of all time. No cardiovascular or vascular surgeon involved in the management of complex aortic diseases can afford, or would want, to be without their own copy.

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Cancer: Principles and Practice of Oncology. 5th ed.

V. T. deVita Jr, S. Hellman and S. A. Rosenberg (eds). 286 × 220 mm. Pp. 3312. Illustrated. 1996. Philadelphia, Pennsylvania: Lippincott-Raven. £160.

DeVita, Hellman and Rosenberg have created the standard reference textbook for cancer treatment and sustained its pre-eminent position through five editions since its first publication in 1982. The formula has been to organize international authorities in the field to provide information about the basic science and treatments that underpin cancer treatment, followed by comprehensive chapters providing full information, from aetiology to results of treatment, for each cancer by anatomical location. It is a unique work that is found in the bookshelves of most oncology departments. I was interested to compare the current edition with the second edition which was published in 1985, both to find how the book had been developing and also to assess changes in cancer treatment. The latest edition is almost 800 pages longer which reflects the addition of more information about the biological background to cancer, both in the Introduction and also in each site specific section. Despite the increased understanding of cancer biology, the bulk of the text is concerned with techniques for mixing chemotherapy, radiotherapy and surgery to provide the best outcome. The increased use of chemotherapy is reflected in a new section concerned with vascular access. It is disappointing that, of the nine novel therapies set out in the newer methods of cancer treatment chapter in the second edition, only one (bone marrow transplantation) has been widely accepted. The latest edition also provides information on nine novel approaches to cancer treatment, most of which are based on recent advances in understanding of cancer biology. As the results of treatment improve, without necessarily providing a cure, and treatments become more expensive, concerns develop about the quality of additional survival and the ability of society to cover the costs. Societal and quality-of-life considerations are discussed in the last section of this textbook, but it is clear there is much more to be learned. The fifth edition of this encyclopaedic work is a worthy successor to the previous editions and will maintain its pre-eminent position.

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Textbook of Endourology

R. E. Sosa, D. M. Albala, A. D. Jenkins and A. P. Perlmutter (eds). 289 × 219 mm. Pp. 650. Illustrated. 1997. Philadelphia, Pennsylvania: W. B. Saunders. £139.

In 2 years it will be the 20th anniversary of the invention of the term *endourology*. Urologists, with the help of radiologists, were among the first specialists to manipulate internal organs without formal skin incisions and, indeed, progress was more limited by the ingenuity and skills of the instrument makers than of the enthusiastic urologists. If we were to relate the wonders of this new type of surgery that has developed logarithmically over the past two decades to some of our predecessors they would be disbelieving.

This book is truly remarkable in its coverage of what is new and exciting in today's urology. It does not simply encompass percutaneous nephrolithotomy and extracorporeal shockwave lithotripsy but also explains the latest in prostatectomy, such as the use of heat, radiowaves, ultrasonography, laser and even electrosurgical vaporization. Technical details abound to the point that some procedures look tantalizingly easy, but then there are headings such as 'Poor visibility during ureteroscopy' and we are reminded of all the times we struggled to achieve a view of even moderate clarity in the early days of endoscopy.

For those in, or wanting to get into, the rapidly changing endourology business, this has to be a book of great topical interest. The authors must have had an extraordinary hold over the large band of contributors to have persuaded them to produce the latest in technical detail that has resulted in such a modern text. There will be many more changes in this type of surgery. I am left accepting that while I might have my renal stones removed percutaneously, I am not so sure that I would have a nephrectomy or radical lymphadenectomy just yet.

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Trauma to the Genito-urinary Tract. A Practical Guide to Management

N. Cetti and R. S. Kirby. 240 × 158 mm. Pp. 72. Illustrated. 1997. Oxford: Butterworth-Heinemann. £19.99.

This excellent new book written by two urologists, one with extensive practical urological experience of modern warfare missile injury, would make a useful addition to any trainee surgeon's book list and should be essential reading for the trainee urologist. It is divided into eight short chapters, each of which consider the problems of the different anatomical areas of the urinary tract, with a separate excellent chapter on missile injury, particularly important with the increased use of high-velocity weapons among the civilian population and with the recent extraordinary reduction in UK armed forces medical personnel. We may all need to be experts in this field before long. Each chapter gives a basic description of the common injuries of the area of the urinary tract in question, with clear and simple line drawings and illustrative radiographs, followed by useful case studies of 'real' patients and the difficulties experienced. Particularly valuable for the trainee are the highlighted text boxes. These keynote 'lessons' every page or two define the main points the authors wish to get across. At the end of the book there is a list of easily obtainable references for further reading, ideal for the higher surgical trainee. This is an excellent little volume. It is well written and is an easy and interesting read. Every accident and emergency doctor and surgical trainee would benefit from reading this work.

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Review of Surgery. 2nd ed.

D. C. Sabiston Jr. (ed.). 279 × 215 mm. Pp. 268. Not illustrated. 1997. Philadelphia, Pennsylvania: W. B. Saunders Company. £25.

The stated purpose of this review of surgery is to provide medical students, residents and practising surgeons with an opportunity to review the field of surgery in preparation for many types of examinations. Dr Sabiston claims that the questions have been written by authorities in the field and they have also provided the appropriate answers. The appropriate authorities are in fact approximately 180 contributors, who are listed on the first four pages of the book. It would appear that the questions are based on Sabiston's *Textbook of Surgery* and *Biological Basis of Modern Surgical Practice.* Without these textbooks of surgery, this book is of little use and would be impossible to plough through. The questions are followed by a series of multiple choice questions. The discussion then outlines the rationale for the correct answers. Many of the questions are very specialized and certainly the answers would not be known by the majority of the people whom this book is aimed at, namely medical students, residents and practising surgeons.

This book might be useful in a library as a companion book to Dr Sabiston's *Textbook of Surgery* However, I do not see medical students or surgeons in training wanting to purchase this for their own use. The book in isolation is a failure but may be of use to people who use Sabiston's *Textbook of Surgery* as their general textbook of surgery.

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British Journal of Surgery 1997, **84**, 1038

Notices and announcements

7–8 July 1997
Rectal Cancer Workshop
Singapore
Information: Y. H. Ho, Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 169608

13 July–22 August 1997
International Medical Students' Summer School
Manchester, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

16–18 July 1997
British Association of Surgical Oncology 54th Scientific Meeting
Aberdeen, UK
Information. V. Hall, Administrator, BASO, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

26–27 July 1997
Hong Kong Surgical Forum – Summer 1997
Wanchai, Hong Kong
Information Forum Secretary, Hong Kong Surgical Forum, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

31 August–3 September 1997
19th ESPEN Congress on Clinical Nutrition and Metabolism
Amsterdam, The Netherlands
Information. Van Namen and Westerlaken Congress Organisation Services, PO Box 1558, 6501 BN Nijmegen, The Netherlands

4 September 1997
Total Mesorectal Excision Study Day
Sheffield, UK
Information: C. Stenton, Short Course Officer, Faculty of Medicine, The Medical School, Sheffield S10 2RX, UK

7–12 September 1997
8th International Congress on Cleft Palate and Related Craniofacial Anomalies
Singapore
Information: Dr L. Keuk, Organising Committee, Academy of Medicine, 16 College Road, Singapore 0316

12–17 October 1997
Management of Emergencies and Disasters: a Multidisciplinary Approach
Stoke, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

12–18 October 1997
Telemedicine and Telecare
Belfast, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

15–22 October 1997
Cancer in Children: Challenges and Controversies
London, UK
Information. Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

23–24 October 1997
2nd Nottingham International Colorectal Cancer Symposium
Nottingham, UK
Information. J. D. Hardcastle, Department of Surgery, University Hospital, Nottingham NG7 2UH, UK

6–19 November 1997
Hong Kong International Cancer Conference and Asian Pacific Cancer Congress 1997
Hong Kong
Information. Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

9–14 November 1997
Health Technology Assessment: the Pathway to Evidence-Based Practice – the UK Experience
Manchester, UK
Information: Promotions Manager, International Seminars, The British Council, 1 Beaumont Place, Oxford OX1 2PJ, UK

27–28 November 1997
31st Meeting of the Vascular Surgical Society of Great Britain and Ireland
London, UK
Information. T Szymanska, Vascular Surgical Society of Great Britain and Ireland, Countess of Chester Hospital, Liverpool Road, Chester CH2 1BQ, UK

25 February–1 March 1998
IX Asean Congress of Plastic Surgery
Penang, Malaysia
Information: M Subramaniam, Department of Plastic Surgery, Hospital Ipoh, 30990 Ipoh, Perak, Malaysia

20–22 April 1998
The Paediatric Oesophagus. An Interdisciplinary Symposium. Main Topic: Gastro-Oesophageal Reflux with a Special Interest in Alkaline Reflux
Izmir, Turkey
Information. O. Mutaf, Department of Paediatric Surgery, Ege University Faculty of Medicine, 35100 Izmir, Turkey

13–15 May 1998
Association of Surgeons of Great Britain and Ireland
Edinburgh, UK
Information Association of Surgeons of Great Britain and Ireland, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

20–24 June 1998
Therapeutic Options for the Locally Advanced Non-Small Cell Lung Cancer
Terme di Valdieri, Italy
Information. G. Buccheri, Scientific Secretary, Ospedale A. Carle, 1-12100 Roccavione (CN), Italy

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted All manuscripts are submitted to editorial review.

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another journal, has not been accepted for publication elsewhere and has not already been published. **Any detected attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** In order to avoid subsequent embarrassment, authors are requested to submit with their manuscript copies of any other papers, either published, in press, or submitted for consideration elsewhere, which relate to the same subject. It is essential that publications or submissions using the same data set should be submitted to the Editors to allow assessment of any potential overlap with the submission to the Journal. The title page should indicate whether the paper is based on a previous communication to a society or other meeting. Articles and their illustrations become the property of the Journal unless rights are reserved before publication.

Authors are requested to send three copies of original articles and other editorial matter to: The Editor, *The British Journal of Surgery*, Blackwell Science Ltd, 25 John Street, London WC1N 2BL, UK. Telephone: 01714041831. Facsimile: 01714041927. Books for review should be sent to the same address.

A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state whether an abstract of the work has been published and an appropriate reference should be given on the title page. Authors must disclose in the covering letter any potential or actual personal, political or financial interest they may have in the material, information or techniques described in the paper. The decision to publish or withhold such information will be made by the Editor. Sources of financial support for the work should also be acknowledged. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents. The Journal accepts the criteria for authorship proposed in the *British Medical Journal* (*BMJ* 1994; 308: 39–42). When a paper has many authors, they may be asked to justify the inclusion of all names listed. Results of multicentre studies should be reported under the name of the organizing study group. Methods of recognizing contributors have been proposed (*Lancet* 1995; 345· 668).

Following final approval of articles, authors are asked to submit the accepted version on disk. These should be IBM-compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, software, and disk system if known. **Do not justify.** Particular attention should be taken to ensure that any articles submitted adhere **exactly** to Journal style in all respects. Please send us digital versions of your figures. Ideally, these should be sent in native format or PICT if created on a Mac, or in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them Avoid using tints if possible; if they are essential to the understanding of the figure, try to make them coarse. Further details can be obtained from the publisher. Disks will not be returned to authors.

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Ethics

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethics committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs that might identify an individual. Evidence of such consent should be submitted with the manuscript.

Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts, which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; 296: 401–5 or the *Annals of Internal Medicine* 1988; 108: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the brief name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal believes that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a abstract of no more than 200 words on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation. **Randomized controlled trials** should be clearly identified as such in the title and abstract.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery* These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no abstract is required Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 400 words (300 if accompanied by a figure), with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications that may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4-cm margins. Manuscripts that do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, abstract, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction, methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Abstract

The second page of the manuscript should carry an abstract of not more than 200 words. This should be broken into four paragraphs each with a clear heading as follows. *Background.* this should state why the study was done, and its main aim; *Method:* this should describe patients, laboratory material and other methods used, *Results:* the main findings of the study should be stated briefly, including important numerical values; *Conclusion:* the main conclusion drawn from the Results should be stated. Controversial or unexpected observations may be highlighted, but this section should be brief The summary should identify clearly the nature of the study· randomized controlled trial, retrospective review, experimental study, etc. It should be written in clear prose.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. Line drawings are acceptable as clear black on white graphics, computer printout or photocopies. Radiographs, photomicrographs, etc should be submitted in the form of glossy prints, original transparencies or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. If a table or an illustration has been reproduced from a published work the original source must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension by the reader. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e g 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, references should be numbered consecutively by superscript.[1] or [1–3]. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; 66: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher, year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications.* New York: Springer, 1981: 123–63

Statistics

For detailed guidance on the handling of statistical material, authors should consult *Br J Surg* 1991; 78: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of data, the *analysis* of data and the *interpretation* of results

Design

Authors should set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen endpoints, and explain the rationale for the choice of sample size

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished Use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the *P* value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual *P* values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant' Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data